ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 25 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

The powder is white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Enbrel in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Enbrel can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Enbrel, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis (AS)
Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis
Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

4.2 Posology and method of administration

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients treated with Enbrel should be given the Patient Card.

Enbrel is available in strengths of 10, 25 and 50 mg.

Posology

Rheumatoid arthritis
25 mg Enbrel administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis
The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque psoriasis
The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Special populations

Renal and hepatic impairment
No dose adjustment is required.

Elderly
No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

Paediatric population
The safety and efficacy of Enbrel in children aged less than 2 years has not been established.
No data are available.

Juvenile idiopathic arthritis
The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.

The 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of Enbrel in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age 6 years and above)
The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of Enbrel in children aged below 6 years in the indication plaque psoriasis.

Method of administration

Enbrel is administered by subcutaneous injection. Enbrel powder for solution must be reconstituted in 1 ml of solvent before use (see section 6.6).

Comprehensive instructions for the preparation and administration of the reconstituted Enbrel vial are given in the package leaflet, section 7, "Instructions for use." Detailed instructions on unintentional dosing or scheduling variations, including missed doses, are provided in section 3 of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with Enbrel should not be initiated in patients with active infections, including chronic or localised infections.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the brand name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections

Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of Enbrel (see section 4.8). These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. The safety and efficacy of Enbrel in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

Tuberculosis

Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with Enbrel.

Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the Patient Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Enbrel therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis

therapy before the initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including Enbrel, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with Enbrel. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Enbrel in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, Enbrel should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving Enbrel. Enbrel should be used with caution in patients with a history of hepatitis C.

Concurrent treatment with anakinra

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of Enbrel and anakinra is not recommended (see sections 4.5 and 4.8).

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

Allergic reactions

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella

virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of Enbrel in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Enbrel, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Skin cancers
Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving Enbrel compared with control patients, particularly in patients with psoriasis.

Vaccinations

Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. In a double-blind, placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving Enbrel. The clinical significance of this is unknown.

Autoantibody formation

Treatment with Enbrel may result in the formation of autoimmune antibodies (see section 4.8).

Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment.

Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, Enbrel was not efficacious, and the mortality rate in patients treated with Enbrel was significantly higher after 6 months. Consequently, Enbrel should not

be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Enbrel in patients who also have moderate to severe alcoholic hepatitis.

Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener's granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener's granulomatosis.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Special populations

Elderly
In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received Enbrel were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Paediatric population

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy (see Vaccinations, above).

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with anakinra

Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data).

In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel (see sections 4.4 and 4.8). The combination Enbrel and anakinra has not demonstrated increased clinical benefit, and is therefore not recommended.

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

Concurrent treatment with sulfasalazine

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in

mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

Non-interactions

In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy.

Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Enbrel should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Enbrel during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother’s last dose of Enbrel is generally not recommended.

Breast-feeding

In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Limited information from the published literature indicates etanercept has been detected at low levels in human milk. Etanercept could be considered for use during breast-feeding taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

While systemic exposure in a breastfed infant is expected to be low because etanercept is largely degraded in the gastrointestinal tract, limited data regarding systemic exposure in the breastfed infant are available. Therefore, the administration of live vaccines (e.g., BCG) to a breastfed infant when the

mother is receiving etanercept could be considered 16 weeks after stopping breast-feeding (or at an earlier timepoint if the infant etanercept serum levels are undetectable).

Fertility

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

4.7 Effects on ability to drive and use machines

Enbrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), headache, allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for Enbrel. TNF-antagonists, such as Enbrel, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with Enbrel. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of Enbrel, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with Enbrel use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Very Rare < 1/10,000**	**Not Known (Cannot be Estimated from Available Data)**
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)*		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic infection)*	Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*		Hepatitis B reactivation, listeria
Neoplasms benign, malignant and			Non-melanoma skin cancers* (see section 4.4)	Malignant melanoma (see section 4.4),		Merkel cell carcinoma (see

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
unspecified (including cysts and polyps)				lymphoma, leukaemia		section 4.4), Kaposi's sarcoma
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia*	Aplastic anaemia*	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders		Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*	Vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis)	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis		Worsening of symptoms of dermatomyositis
Nervous system disorders	Headache			CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive (see section 4.4)	New onset cardiac failure congestive (see section 4.4)		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*		
Gastrointestinal disorders			Inflammatory bowel disease			
Hepatobiliary disorders			Elevated liver enzymes*	Autoimmune hepatitis*		
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash	Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions	Toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus, subacute cutaneous lupus		

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
				erythematosus, lupus-like syndrome		
Renal and urinary disorders				Glomerulonephritis		
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*	Pyrexia				

*see Description of selected adverse reactions, below.

Description of selected adverse reactions

Malignancies and lymphoproliferative disorders
One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. In a group of 2,711 plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

Injection site reactions
Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with Enbrel developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Serious infections
In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at

various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, *Streptococcal* fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Enbrel treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with Enbrel, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received Enbrel. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida, Pneumocystis*, *Aspergillus,* and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

Autoantibodies
Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

Pancytopenia and aplastic anaemia
There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

Interstitial lung disease
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Concurrent treatment with anakinra
In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

Elevated liver enzymes
In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

Autoimmune hepatitis
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

Undesirable effects in paediatric patients with plaque psoriasis
In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Enbrel subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Enbrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells, including T-cells, leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etanercept, possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, two studies in adults with non-radiographic axial spondyloarthritis, four studies in adults with plaque psoriasis, three studies in juvenile idiopathic arthritis and one study in paediatric patients with plaque psoriasis.

Adult patients with rheumatoid arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively: ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; $p<0.01$ Enbrel vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

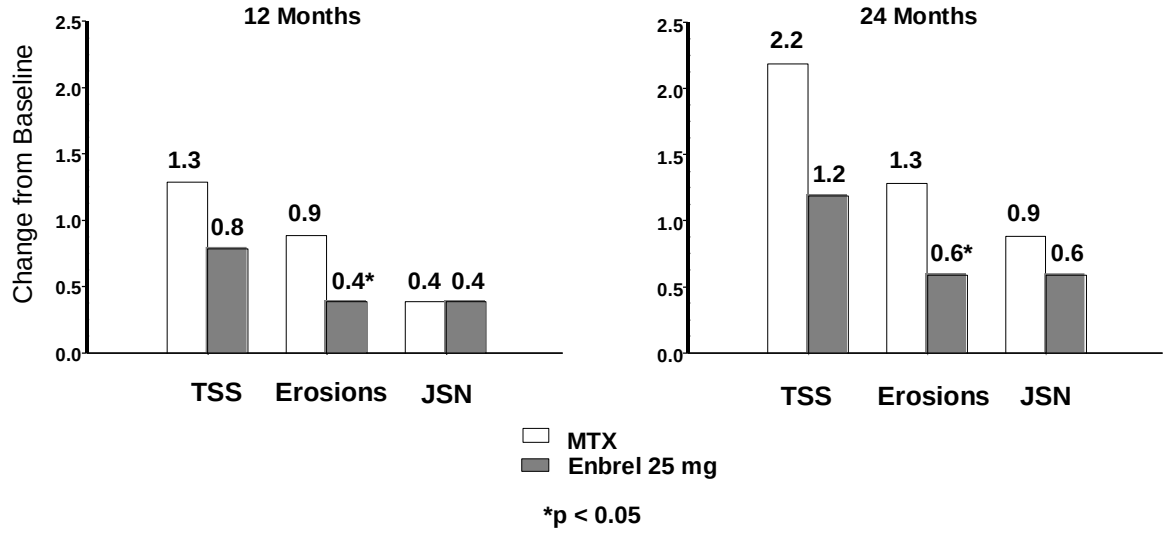
Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Enbrel was significantly better than placebo in all components of the ACR criteria, as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with Enbrel compared to controls at 3 and 6 months.

After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received Enbrel without interruption.

The efficacy of Enbrel was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Enbrel were administered subcutaneously (SC) twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement, including onset of action within 2 weeks with Enbrel 25 mg, was similar to that seen in the previous trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

Radiographic Progression: Comparison of Enbrel vs. Methotrexate in Patients with RA of <3 Years Duration



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months.

Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
ACR Responses[a]			
ACR 20	58.8%	65.5%	74.5% †,ϕ
ACR 50	36.4%	43.0%	63.2% †,ϕ
ACR 70	16.7%	22.0%	39.8% †,ϕ
DAS			
Baseline score[b]	5.5	5.7	5.5
Week 52 score[b]	3.0	3.0	2.3†,ϕ
Remission[c]	14%	18%	37%†,ϕ

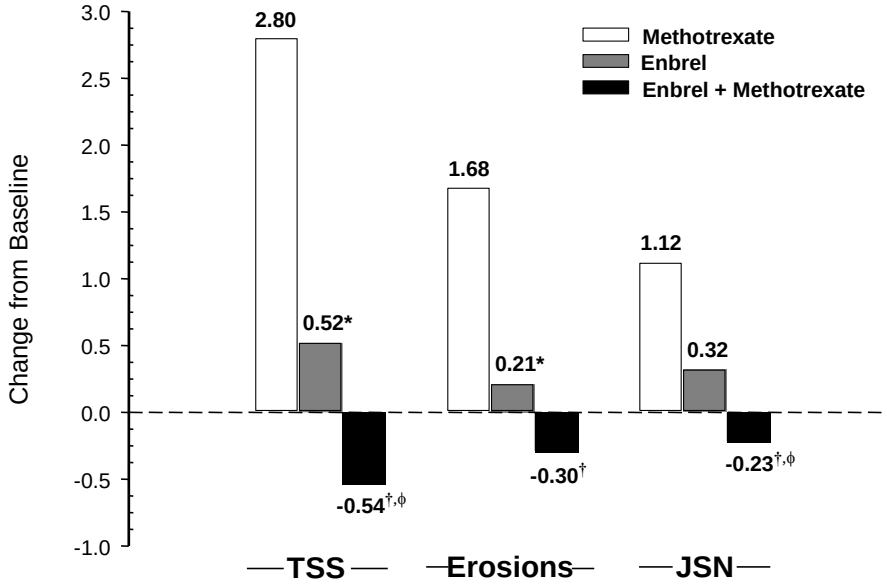
Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
HAQ			
Baseline	1.7	1.7	1.8
Week 52	1.1	1.0	$0.8^{\dagger,\phi}$

a: Patients who did not complete 12 months in the study were considered to be non-responders.
b: Values for Disease Activity Score (DAS) are means.
c: Remission is defined as DAS <1.6.
Pairwise comparison p-values: † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. Enbrel.

Radiographic progression at 12 months was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

Radiographic Progression: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of Enbrel vs. methotrexate, † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. Enbrel.

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p<0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p<0.05$). Among patients who completed a

full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens.

Adult patients with psoriatic arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients had previously been treated with NSAIDs (86%), DMARDs (80%), and corticosteroids (24%). Patients currently on methotrexate therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week methotrexate. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

Clinical responses were expressed as percentages of patients achieving the ACR 20, 50, and 70 response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table below.

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

	Percent of Patients	
	Placebo	Enbrel[a]
Psoriatic Arthritis Response	n = 104	n = 101
ACR 20		
Month 3	15	59[b]
Month 6	13	50[b]
ACR 50		
Month 3	4	38[b]
Month 6	4	37[b]
ACR 70		
Month 3	0	11[b]
Month 6	1	9[c]
PsARC		
Month 3	31	72[b]
Month 6	23	70[b]

a: 25 mg Enbrel SC twice weekly
b: $p < 0.001$, Enbrel vs. placebo
c: $p < 0.01$, Enbrel vs. placebo

Among patients with psoriatic arthritis who received Enbrel, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Enbrel was significantly better than placebo in all measures of disease activity ($p < 0.001$), and responses were

similar with and without concomitant methotrexate therapy. Quality of life in psoriatic arthritis patients was assessed at every timepoint using the disability index of the HAQ. The disability index score was significantly improved at all timepoints in psoriatic arthritis patients treated with Enbrel, relative to placebo ($p < 0.001$).

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in the table below. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 12 months was higher in the Enbrel group compared with the placebo group (73% vs. 47%, respectively, $p \leq 0.001$). The effect of Enbrel on radiographic progression was maintained in patients who continued on treatment during the second year. The slowing of peripheral joint damage was observed in patients with polyarticular symmetrical joint involvement.

Mean (SE) Annualized Change from Baseline in Total Sharp Score

Time	Placebo (n = 104)	Etanercept (n = 101)
Month 12	1.00 (0.29)	-0.03 (0.09)[a]

SE = standard error.
a. p = 0.0001.

Enbrel treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of Enbrel in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.
No study has been performed in patients with psoriatic arthritis using the 50 mg once-weekly dosing regimen. Evidence of efficacy for the once-weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

Adult patients with ankylosing spondylitis
The efficacy of Enbrel in ankylosing spondylitis was assessed in 3 randomised, double-blind studies comparing twice-weekly administration of 25 mg Enbrel with placebo. A total of 401 patients were enrolled, from which 203 were treated with Enbrel. The largest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months in 138 patients.

The primary measure of efficacy (ASAS 20) was a ≥20% improvement in at least 3 of the 4 Assessment in Ankylosing Spondylitis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and absence of deterioration in the remaining domain. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% improvement, respectively.

Compared to placebo, treatment with Enbrel resulted in significant improvements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of therapy.

Responses of Patients with Ankylosing Spondylitis in a Placebo-controlled Trial		
	Percent of Patients	
Ankylosing Spondylitis Response	Placebo N = 139	Enbrel N = 138
ASAS 20		
2 weeks	22	46[a]
3 months	27	60[a]
6 months	23	58[a]
ASAS 50		
2 weeks	7	24[a]
3 months	13	45[a]
6 months	10	42[a]
ASAS 70		
2 weeks	2	12[b]
3 months	7	29[b]
6 months	5	28[b]
a: p <0.001, Enbrel vs. placebo		
b: p = 0.002, Enbrel vs. placebo		

Among patients with ankylosing spondylitis who received Enbrel, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly vs. 25 mg Enbrel administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once-weekly and 25 mg twice-weekly regimens were similar.

Adult patients with non-radiographic axial spondyloarthritis

Study 1
The efficacy of Enbrel in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received Enbrel 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. The double-blind period was followed by an open-label period during which all patients receive Enbrel 50 mg weekly for up to an additional 92 weeks. MRIs of the sacroiliac joint and spine were obtained to assess inflammation at baseline and at weeks 12 and 104.

Compared to placebo, treatment with Enbrel resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

Efficacy Response in Placebo-Controlled nr-AxSpa Study: Percent of Patients Achieving Endpoints

Double-Blind Clinical Responses at Week 12	Placebo N=106 to 109*	Enbrel N=103 to 105*
ASAS** 40	15.7	32.4[b]
ASAS 20	36.1	52.4[c]
ASAS 5/6	10.4	33.0[a]
ASAS partial remission	11.9	24.8[c]
BASDAI***50	23.9	43.8[b]

*Some patients did not provide complete data for each endpoint
**ASAS=Assessments in Spondyloarthritis International Society
***Bath Ankylosing Spondylitis Disease Activity Index
a: p <0.001, b:<0.01 and c:<0.05, respectively between Enbrel and placebo

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint (SIJ) as measured by MRI for patients receiving Enbrel. Adjusted mean change from baseline was 3.8 for Enbrel treated (n=95) versus 0.8 for placebo treated (n=105) patients (p<0.001). At week 104, the mean change from baseline in the SPARCC score measured on MRI for all Enbrel-treated subjects was 4.64 for the SIJ (n=153) and 1.40 the spine (n=154).

Enbrel showed statistically significantly greater improvement from baseline to week 12 compared to placebo in most health-related quality of life and physical function assessments, including BASFI (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D Overall Health State Score and SF-36 Physical Component Score.

Clinical responses among nr-AxSpa patients who received Enbrel were apparent at the time of the first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings. At week 104, 8 subjects had progressed to a score of bilateral Grade 2 on spinal X-ray according to the modified New York Radiological Grade, indicative of axial spondyloarthropathy.

Study 2
This multi-center, open-label, phase 4, 3-period study evaluated the withdrawal and retreatment of Enbrel in patients with active nr-AxSpa who achieved an adequate response (inactive disease defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP) less than 1.3) following 24 weeks of treatment.

209 adult patients with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the Assessment of SpondyloArthritis International Society (ASAS) classification criteria of axial spondyloarthritis (but not meeting the modified New York criteria for AS), having positive MRI findings (active inflammation on MRI highly suggestive of sacroiliitis associated with SpA) and/or positive hsCRP (defined as high sensitivity C-reactive protein [hsCRP] > 3 mg/l), and active symptoms defined by an ASDAS CRP greater than or equal to 2.1 at the screening visit received open-label Enbrel 50 mg weekly plus stable background NSAID at the optimal tolerated anti-inflammatory dosage for 24 weeks in Period 1. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. At week 24, 119 (57%) patients achieved inactive disease and entered into the Period 2 40-week withdrawal phase where subjects discontinued etanercept, yet maintained the background NSAID. The primary measure of efficacy was the occurrence of flare (defined as an ASDAS erythrocyte sedimentation rate (ESR) greater than or equal to 2.1) within 40 weeks following withdrawal of Enbrel. Patients who flared were retreated with Enbrel 50 mg weekly for 12 weeks (Period 3).

In Period 2, the proportion of patients experiencing ≥1 flare increased from 22% (25/112) at week 4 to 67% (77/115) at week 40. Overall, 75% (86/115) patients experienced a flare at any time point within 40 weeks following withdrawal of Enbrel.

The key secondary objective of Study 2 was to estimate time to flare after withdrawal of Enbrel and additionally compare the time to flare to patients from Study 1 who met the Study 2 withdrawal phase entry requirements and continued Enbrel therapy.

The median time to flare following withdrawal of Enbrel was 16 weeks (95% CI: 13-24 weeks). Less than 25% of patients in Study 1 who did not have treatment withdrawn experienced a flare over the equivalent 40-weeks as in Period 2 Study 2. The time to flare was statistically significantly shorter in subjects who discontinued Enbrel treatment (Study 2) compared to subjects who received continuous etanercept treatment (Study 1), $p<0.0001$.

Of the 87 patients who entered Period 3 and were retreated with Enbrel 50 mg weekly for 12 weeks, 62% (54/87) reachieved inactive disease, with 50% of them reachieving it within 5 weeks (95% CI: 4-8 weeks).

Adult patients with plaque psoriasis
Enbrel is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least one of the three major systemic therapies as available.

The efficacy of Enbrel versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing Enbrel with other systemic therapies. Instead, the safety and efficacy of Enbrel were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

Study 1 was a Phase 2 study in patients with active, but clinically stable, plaque psoriasis involving ≥ 10% of the body surface area who were ≥ 18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of Enbrel (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. Enbrel was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three Enbrel doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded Enbrel (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg Enbrel, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg Enbrel twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg Enbrel or placebo once weekly for 12 weeks and then all patients received open-label 50 mg Enbrel once weekly for an additional 12 weeks.

In study 1, the Enbrel-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) ($p<0.0001$). At 24 weeks, 56% of patients in the Enbrel-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

Responses of Patients with Psoriasis in Studies 2, 3 and 4

	Study 2					Study 3			Study 4	
		----------Enbrel---------				--------Enbrel-------			-------Enbrel------	
		25 mg BIW		50 mg BIW			25 mg BIW	50 mg BIW	50 mg QW	50 mg QW
Response (%)	Placebo n = 166 wk 12	n = 162 wk 12	n = 162 wk 24[a]	n = 164 wk 12	n = 164 wk 24[a]	Placebo n = 193 wk 12	n = 196 wk 12	n = 196 wk 12	Placebo n = 46 wk 12	n = 96 wk 12	n = 90 wk 24[a]
PASI 50	14	58*	70	74*	77	9	64*	77*	9	69*	83
PASI 75	4	34*	44	49*	59	3	34*	49*	2	38*	71
DSGA[b], clear or almost clear	5	34*	39	49*	55	4	39*	57*	4	39*	64

*$p \leq 0.0001$ compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving Enbrel 25 mg BIW or 50 mg once weekly from week 13 to week 24.

b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received Enbrel, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned, with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with Enbrel in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Enbrel dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the Enbrel-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) ($p< 0.0001$). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where Enbrel was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

Antibodies to Enbrel

Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
The safety and efficacy of Enbrel were assessed in a two-part study in 69 children with polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic onset). Patients aged 4 to 17 years with moderately to severely active polyarticular-course juvenile idiopathic arthritis refractory to, or intolerant of, methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomised to remain on Enbrel or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥ 30% worsening in three of six JRA core set criteria and ≥ 30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrollment) continued to receive Enbrel for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

Long-term safety of Enbrel monotherapy (n=103), Enbrel plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study (n=127), 60 patients with extended oligoarthritis (EO) (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with Enbrel at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender

joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Of the 127 patients in the parent study, 109 participated in the open-label extension study and were followed for an additional 8 years for a total of up to 10 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Enbrel, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Enbrel following an earlier withdrawal from treatment; and 45 (41%) had stopped Enbrel (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire follow-up period. Patients actively taking Enbrel could enter an optional withdrawal-retreatment period once during the extension study based on investigator's judgement of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥ 30% worsening in at least 3 of the 6 ACR Pedi components with ≥ 30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after Enbrel withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the small number of data points, these results should be interpreted with caution.

The safety profile was consistent with that observed in the parent study.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy. Additionally, studies have not been conducted to assess the effects of reducing the recommended dose of Enbrel following its long-term use in patients with JIA.

Paediatric patients with plaque psoriasis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by an sPGA score ≥ 3, involving ≥ 10% of the BSA, and PASI ≥ 12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received Enbrel 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to Enbrel had positive efficacy responses (e.g., PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks

	Enbrel 0.8 mg/kg Once Weekly (N = 106)	**Placebo (N = 105)**
PASI 75, n (%)	60 (57%)[a]	12 (11%)
PASI 50, n (%)	79 (75%)[a]	24 (23%)
sPGA "clear" or "minimal", n (%)	56 (53%)[a]	14 (13%)

Abbreviation: sPGA-static Physician Global Assessment
a. $p < 0.0001$ compared with placebo

After the 12-week double-blind treatment period, all patients received Enbrel 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to Enbrel. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of Enbrel 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with Enbrel was generally comparable to the original 48-week study and did not reveal any new safety findings.

5.2 Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products, as well as the parent compound.

Absorption

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 μg/ml, and the area under the curve was 235 ± 96.6 μg•hr/ml.

Mean serum concentration profiles at steady state in treated RA patients were C_{max} of 2.4 mg/l vs. 2.6 mg/l, C_{min} of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg Enbrel once weekly (n=21) vs. 25 mg Enbrel twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466 μg•hr/ml and 474 μg•hr/ml for 50 mg Enbrel once weekly (N= 154) and 25 mg twice weekly (N = 148), respectively.

Distribution

A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of Enbrel in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.

There is no apparent pharmacokinetic difference between males and females.

Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

Special populations

Renal impairment
Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal failure. The presence of renal impairment should not require a change in dosage.

Hepatic impairment
Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

Elderly
The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
In a polyarticular-course juvenile idiopathic arthritis trial with Enbrel, 69 patients (aged 4 to 17 years) were administered 0.4 mg Enbrel/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Paediatric patients with plaque psoriasis
Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice-weekly.

5.3 Preclinical safety data

In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with Enbrel due to the development of neutralising antibodies in rodents.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Mannitol (E421)
Sucrose
Trometamol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

Chemical and physical in-use stability has been demonstrated for 6 hours at temperatures of up to 25°C after reconstitution. From a microbiological point of view, the reconstituted medicinal product should be used immediately. If not used immediately, storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at temperatures of up to 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Enbrel may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks of removal from refrigeration.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear glass vial (2 ml, type I glass) with rubber stoppers, aluminium seals, and flip-off plastic caps. Cartons contain 4 vials of Enbrel with 8 alcohol swabs.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

Enbrel is reconstituted with 1 ml water for injections before use and administered by subcutaneous injection. Enbrel contains no antibacterial preservative, and therefore, solutions prepared with water for injections should be administered as soon as possible and within 6 hours following reconstitution. The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes or particles. Some white foam may remain in the vial – this is normal. Enbrel should not be used if all the powder in the vial is not dissolved within 10 minutes. If this is the case, start again with another vial.

Comprehensive instructions for the preparation and administration of the reconstituted Enbrel vial are given in the package leaflet, section 7, “Instructions for use.”

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2000
Date of last renewal: 26 November 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 25 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (powder for injection).

The powder is white. The solvent is a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Enbrel in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Enbrel can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Enbrel, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis (AS)
Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis
Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

4.2 Posology and method of administration

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients treated with Enbrel should be given the Patient Card.

Enbrel is available in strengths of 10, 25 and 50 mg.

Posology

Rheumatoid arthritis
25 mg Enbrel administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis
The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque psoriasis
The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Special populations

Renal and hepatic impairment
No dose adjustment is required.

Elderly
No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

Paediatric population
The safety and efficacy of Enbrel in children aged less than 2 years has not been established.
No data are available.

Juvenile idiopathic arthritis
The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.

The 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of Enbrel in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age 6 years and above)
The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of Enbrel in children aged below 6 years in the indication plaque psoriasis.

Method of administration

Enbrel is administered by subcutaneous injection. Enbrel powder for solution must be reconstituted in 1 ml of solvent before use (see section 6.6).

Comprehensive instructions for the preparation and administration of the reconstituted Enbrel vial are given in the package leaflet, section 7, "Instructions for use." Detailed instructions on unintentional dosing or scheduling variations, including missed doses, are provided in section 3 of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with Enbrel should not be initiated in patients with active infections, including chronic or localised infections.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the brand name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections

Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of Enbrel (see section 4.8). These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. The safety and efficacy of Enbrel in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

Tuberculosis

Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with Enbrel.

Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the Patient Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Enbrel therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis

therapy before the initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including Enbrel, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with Enbrel. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Enbrel in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, Enbrel should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving Enbrel. Enbrel should be used with caution in patients with a history of hepatitis C.

Concurrent treatment with anakinra

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of Enbrel and anakinra is not recommended (see sections 4.5 and 4.8).

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

Allergic reactions

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated.

The rubber tip cap (closure) of the diluent syringe contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled by, or when Enbrel is administered to, persons with known or possible latex sensitivity.

Immunosuppression

The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of Enbrel in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Enbrel, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Skin cancers
Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving Enbrel compared with control patients, particularly in patients with psoriasis.

Vaccinations

Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. In a double-blind, placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving Enbrel. The clinical significance of this is unknown.

Autoantibody formation

Treatment with Enbrel may result in the formation of autoimmune antibodies (see section 4.8).

Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment.

Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, Enbrel was not efficacious, and the mortality rate in patients treated with Enbrel was significantly higher after 6 months. Consequently, Enbrel should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Enbrel in patients who also have moderate to severe alcoholic hepatitis.

Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener's granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener's granulomatosis.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Special populations

Elderly
In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received Enbrel were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Paediatric population

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy (see Vaccinations, above).

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with anakinra

Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data).

In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel (see sections 4.4 and 4.8). The combination Enbrel and anakinra has not demonstrated increased clinical benefit, and is therefore not recommended.

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

Concurrent treatment with sulfasalazine

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

Non-interactions

In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy.

Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Enbrel should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Enbrel during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother’s last dose of Enbrel is generally not recommended.

Breast-feeding

In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Limited information from the published literature indicates etanercept has been detected at low levels in human milk. Etanercept could be considered for use during breast-feeding taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

While systemic exposure in a breastfed infant is expected to be low because etanercept is largely degraded in the gastrointestinal tract, limited data regarding systemic exposure in the breastfed infant are available. Therefore, the administration of live vaccines (e.g., BCG) to a breastfed infant when the mother is receiving etanercept could be considered 16 weeks after stopping breast-feeding (or at an earlier timepoint if the infant etanercept serum levels are undetectable).

Fertility

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

4.7 Effects on ability to drive and use machines

Enbrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), headache, allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for Enbrel. TNF-antagonists, such as Enbrel, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with Enbrel. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of Enbrel, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with Enbrel use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Very Rare < 1/10,000**	**Not Known (Cannot be Estimated from Available Data)**
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis,		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic	Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and		Hepatitis B reactivation, listeria

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
	skin infection)*		infection)*	Legionella)*		
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers* (see section 4.4)	Malignant melanoma (see section 4.4), lymphoma, leukaemia		Merkel cell carcinoma (see section 4.4), Kaposi's sarcoma
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia*	Aplastic anaemia*	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders		Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*	Vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis)	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis		Worsening of symptoms of dermatomyositis
Nervous system disorders	Headache			CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive (see section 4.4)	New onset cardiac failure congestive (see section 4.4)		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*		
Gastrointestinal disorders			Inflammatory bowel disease			
Hepatobiliary disorders			Elevated liver enzymes*	Autoimmune hepatitis*		

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash	Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions	Toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome		
Renal and urinary disorders				Glomerulonephritis		
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*	Pyrexia				

*see Description of selected adverse reactions, below.

Description of selected adverse reactions

Malignancies and lymphoproliferative disorders
One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. In a group of 2,711 plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

Injection site reactions
Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most

recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with Enbrel developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Serious infections
In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, *Streptococcal* fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Enbrel treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with Enbrel, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received Enbrel. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida, Pneumocystis, Aspergillus,* and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

Autoantibodies
Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

Pancytopenia and aplastic anaemia
There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

Interstitial lung disease
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Concurrent treatment with anakinra
In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

Elevated liver enzymes
In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

Autoimmune hepatitis
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients

were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

Undesirable effects in paediatric patients with plaque psoriasis
In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Enbrel subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Enbrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells, including T-cells, leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etanercept, possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, two studies in adults with non-radiographic axial spondyloarthritis, four studies in adults with plaque psoriasis, three studies in juvenile idiopathic arthritis and one study in paediatric patients with plaque psoriasis.

Adult patients with rheumatoid arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively: ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; $p < 0.01$ Enbrel vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Enbrel was significantly better than placebo in all components of the ACR criteria, as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with Enbrel compared to controls at 3 and 6 months.

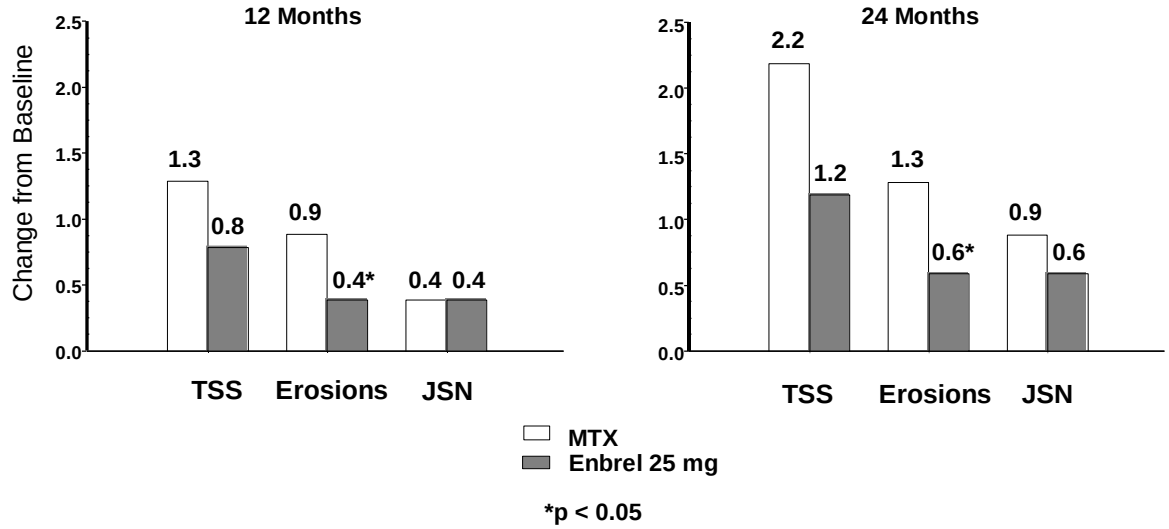
After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received Enbrel without interruption.

The efficacy of Enbrel was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (< 3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Enbrel were administered subcutaneously (SC) twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement, including onset of action within 2 weeks with Enbrel 25 mg, was similar to that seen in the previous trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44%

of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

Radiographic Progression: Comparison of Enbrel vs. Methotrexate in Patients with RA of <3 Years Duration



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months.

Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
ACR Responses[a]			
ACR 20	58.8%	65.5%	74.5% †,ϕ
ACR 50	36.4%	43.0%	63.2% †,ϕ
ACR 70	16.7%	22.0%	39.8% †,ϕ

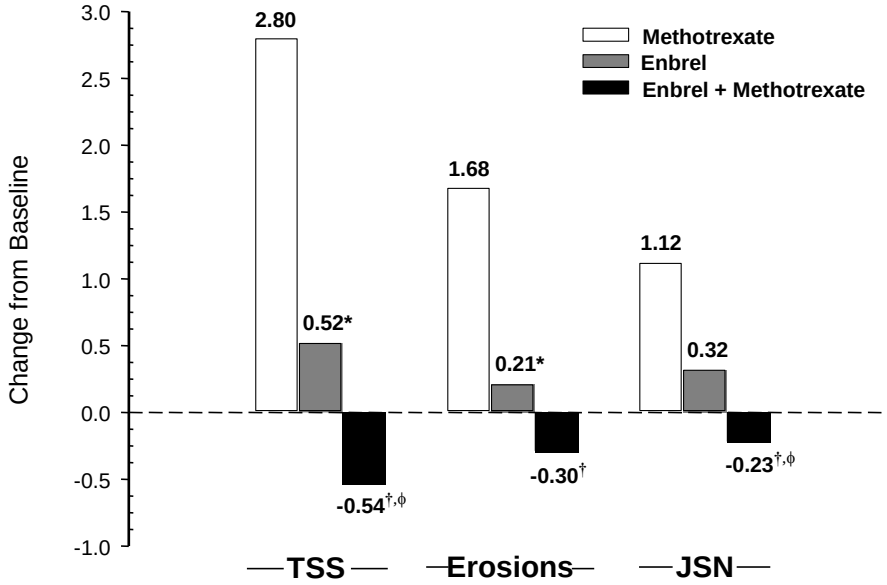
Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
DAS			
Baseline score[b]	5.5	5.7	5.5
Week 52 score[b]	3.0	3.0	2.3†,ϕ
Remission[c]	14%	18%	37%†,ϕ
HAQ			
Baseline	1.7	1.7	1.8
Week 52	1.1	1.0	0.8†,ϕ

a: Patients who did not complete 12 months in the study were considered to be non-responders.
b: Values for Disease Activity Score (DAS) are means.
c: Remission is defined as DAS <1.6.
Pairwise comparison p-values: † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. Enbrel.

Radiographic progression at 12 months was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

Radiographic Progression: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of Enbrel vs. methotrexate, † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. Enbrel.

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p < 0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p < 0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens.

Adult patients with psoriatic arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients had previously been treated with NSAIDs (86%), DMARDs (80%), and corticosteroids (24%). Patients currently on methotrexate therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week methotrexate. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

Clinical responses were expressed as percentages of patients achieving the ACR 20, 50, and 70 response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table below.

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

	Percent of Patients	
	Placebo	Enbrel[a]
Psoriatic Arthritis Response	n = 104	n = 101
ACR 20		
Month 3	15	59[b]
Month 6	13	50[b]
ACR 50		
Month 3	4	38[b]
Month 6	4	37[b]
ACR 70		
Month 3	0	11[b]
Month 6	1	9[c]

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

	Percent of Patients	
	Placebo	Enbrel[a]
Psoriatic Arthritis Response	n = 104	n = 101
PsARC		
Month 3	31	72[b]
Month 6	23	70[b]

a: 25 mg Enbrel SC twice weekly
b: $p < 0.001$, Enbrel vs. placebo
c: $p < 0.01$, Enbrel vs. placebo

Among patients with psoriatic arthritis who received Enbrel, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Enbrel was significantly better than placebo in all measures of disease activity ($p < 0.001$), and responses were similar with and without concomitant methotrexate therapy. Quality of life in psoriatic arthritis patients was assessed at every timepoint using the disability index of the HAQ. The disability index score was significantly improved at all timepoints in psoriatic arthritis patients treated with Enbrel, relative to placebo ($p < 0.001$).

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in the table below. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 12 months was higher in the Enbrel group compared with the placebo group (73% vs. 47%, respectively, $p \leq 0.001$). The effect of Enbrel on radiographic progression was maintained in patients who continued on treatment during the second year. The slowing of peripheral joint damage was observed in patients with polyarticular symmetrical joint involvement.

Mean (SE) Annualized Change from Baseline in Total Sharp Score

	Placebo	Etanercept
Time	(n = 104)	(n = 101)
Month 12	1.00 (0.29)	-0.03 (0.09)[a]

SE = standard error.
a. $p = 0.0001$.

Enbrel treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of Enbrel in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.

No study has been performed in patients with psoriatic arthritis using the 50 mg once-weekly dosing regimen. Evidence of efficacy for the once-weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

Adult patients with ankylosing spondylitis
The efficacy of Enbrel in ankylosing spondylitis was assessed in 3 randomised, double-blind studies comparing twice-weekly administration of 25 mg Enbrel with placebo. A total of 401 patients were enrolled, from which 203 were treated with Enbrel. The largest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the

Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months in 138 patients.

The primary measure of efficacy (ASAS 20) was a ≥20% improvement in at least 3 of the 4 Assessment in Ankylosing Spondylitis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and absence of deterioration in the remaining domain. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% improvement, respectively.

Compared to placebo, treatment with Enbrel resulted in significant improvements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of therapy.

Responses of Patients with Ankylosing Spondylitis in a Placebo-controlled Trial

	Percent of Patients	
Ankylosing Spondylitis Response	Placebo N = 139	Enbrel N = 138
ASAS 20		
2 weeks	22	46[a]
3 months	27	60[a]
6 months	23	58[a]
ASAS 50		
2 weeks	7	24[a]
3 months	13	45[a]
6 months	10	42[a]
ASAS 70		
2 weeks	2	12[b]
3 months	7	29[b]
6 months	5	28[b]
a: p<0.001, Enbrel vs. placebo		
b: p = 0.002, Enbrel vs. placebo		

Among patients with ankylosing spondylitis who received Enbrel, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly vs. 25 mg Enbrel administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once-weekly and 25 mg twice-weekly regimens were similar.

Adult patients with non-radiographic axial spondyloarthritis

Study 1
The efficacy of Enbrel in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate

response or intolerance to two or more NSAIDs. In the double-blind period, patients received Enbrel 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. The double-blind period was followed by an open-label period during which all patients receive Enbrel 50 mg weekly for up to an additional 92 weeks. MRIs of the sacroiliac joint and spine were obtained to assess inflammation at baseline and at weeks 12 and 104.

Compared to placebo, treatment with Enbrel resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

Efficacy Response in Placebo-Controlled nr-AxSpa Study: Percent of Patients Achieving Endpoints

Double-Blind Clinical Responses at Week 12	Placebo N=106 to 109*	Enbrel N=103 to 105*
ASAS** 40	15.7	32.4[b]
ASAS 20	36.1	52.4[c]
ASAS 5/6	10.4	33.0[a]
ASAS partial remission	11.9	24.8[c]
BASDAI***50	23.9	43.8[b]

*Some patients did not provide complete data for each endpoint
**ASAS=Assessments in Spondyloarthritis International Society
***Bath Ankylosing Spondylitis Disease Activity Index
a: p <0.001, b:<0.01 and c:<0.05, respectively between Enbrel and placebo

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint (SIJ) as measured by MRI for patients receiving Enbrel. Adjusted mean change from baseline was 3.8 for Enbrel treated (n=95) versus 0.8 for placebo treated (n=105) patients (p<0.001). At week 104, the mean change from baseline in the SPARCC score measured on MRI for all Enbrel-treated subjects was 4.64 for the SIJ (n=153) and 1.40 the spine (n=154).

Enbrel showed statistically significantly greater improvement from baseline to week 12 compared to placebo in most health-related quality of life and physical function assessments, including BASFI (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D Overall Health State Score and SF-36 Physical Component Score.

Clinical responses among nr-AxSpa patients who received Enbrel were apparent at the time of the first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings. At week 104, 8 subjects had progressed to a score of bilateral Grade 2 on spinal X-ray according to the modified New York Radiological Grade, indicative of axial spondyloarthropathy.

Study 2
This multi-center, open-label, phase 4, 3-period study evaluated the withdrawal and retreatment of Enbrel in patients with active nr-AxSpa who achieved an adequate response (inactive disease defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP) less than 1.3) following 24 weeks of treatment.

209 adult patients with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the Assessment of SpondyloArthritis International Society (ASAS) classification criteria of axial spondyloarthritis (but not meeting the modified New York criteria for AS), having positive MRI findings (active inflammation on MRI highly suggestive of sacroiliitis associated with SpA) and/or positive hsCRP (defined as high sensitivity C-reactive protein [hsCRP] >3 mg/l), and active symptoms

defined by an ASDAS CRP greater than or equal to 2.1 at the screening visit received open-label Enbrel 50 mg weekly plus stable background NSAID at the optimal tolerated anti-inflammatory dosage for 24 weeks in Period 1. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. At week 24, 119 (57%) patients achieved inactive disease and entered into the Period 2 40-week withdrawal phase where subjects discontinued etanercept, yet maintained the background NSAID. The primary measure of efficacy was the occurrence of flare (defined as an ASDAS erythrocyte sedimentation rate (ESR) greater than or equal to 2.1) within 40 weeks following withdrawal of Enbrel. Patients who flared were retreated with Enbrel 50 mg weekly for 12 weeks (Period 3).

In Period 2, the proportion of patients experiencing ≥1 flare increased from 22% (25/112) at week 4 to 67% (77/115) at week 40. Overall, 75% (86/115) patients experienced a flare at any time point within 40 weeks following withdrawal of Enbrel.

The key secondary objective of Study 2 was to estimate time to flare after withdrawal of Enbrel and additionally compare the time to flare to patients from Study 1 who met the Study 2 withdrawal phase entry requirements and continued Enbrel therapy.

The median time to flare following withdrawal of Enbrel was 16 weeks (95% CI: 13-24 weeks). Less than 25% of patients in Study 1 who did not have treatment withdrawn experienced a flare over the equivalent 40-weeks as in Period 2 Study 2. The time to flare was statistically significantly shorter in subjects who discontinued Enbrel treatment (Study 2) compared to subjects who received continuous etanercept treatment (Study 1), $p < 0.0001$.

Of the 87 patients who entered Period 3 and were retreated with Enbrel 50 mg weekly for 12 weeks, 62% (54/87) reachieved inactive disease, with 50% of them reachieving it within 5 weeks (95% CI: 4-8 weeks).

Adult patients with plaque psoriasis
Enbrel is recommended for use in patients as defined in section 4.1. Patients who “failed to respond to” in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least one of the three major systemic therapies as available.

The efficacy of Enbrel versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing Enbrel with other systemic therapies. Instead, the safety and efficacy of Enbrel were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

Study 1 was a Phase 2 study in patients with active, but clinically stable, plaque psoriasis involving ≥ 10% of the body surface area who were ≥ 18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of Enbrel (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. Enbrel was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three Enbrel doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded Enbrel (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg Enbrel, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg Enbrel twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg Enbrel or placebo once weekly for 12 weeks and then all patients received open-label 50 mg Enbrel once weekly for an additional 12 weeks.

In study 1, the Enbrel-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) ($p<0.0001$). At 24 weeks, 56% of patients in the Enbrel-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

Responses of Patients with Psoriasis in Studies 2, 3 and 4

	Study 2					Study 3			Study 4		
		----------Enbrel---------				--------Enbrel-------			-------Enbrel------		
Response (%)	Placebo n = 166 wk 12	25 mg BIW n = 162 wk 12	25 mg BIW n = 162 wk 24[a]	50 mg BIW n = 164 wk 12	50 mg BIW n = 164 wk 24[a]	Placebo n = 193 wk 12	25 mg BIW n = 196 wk 12	50 mg BIW n = 196 wk 12	Placebo n = 46 wk 12	50 mg QW n = 96 wk 12	50 mg QW n = 90 wk 24[a]
PASI 50	14	58*	70	74*	77	9	64*	77*	9	69*	83
PASI 75	4	34*	44	49*	59	3	34*	49*	2	38*	71
DSGA[b], clear or almost clear	5	34*	39	49*	55	4	39*	57*	4	39*	64

*$p \leq 0.0001$ compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving Enbrel 25 mg BIW or 50 mg once weekly from week 13 to week 24.

b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received Enbrel, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned, with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with Enbrel in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Enbrel dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the Enbrel-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) ($p<0.0001$). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where Enbrel was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

Antibodies to Enbrel
Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8 % of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
The safety and efficacy of Enbrel were assessed in a two-part study in 69 children with polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic onset). Patients aged 4 to 17 years with moderately to severely active polyarticular-course juvenile idiopathic arthritis refractory to, or intolerant of, methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomised to remain on Enbrel or receive placebo for four months and assessed for disease flare. Responses were measured using ACR Pedi 30, defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥ 30% worsening in three of six JRA core set criteria and ≥ 30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrollment) continued to receive Enbrel for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

Long-term safety of Enbrel monotherapy (n=103), Enbrel plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years

with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study (n=127), 60 patients with extended oligoarthritis (EO) (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with Enbrel at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Of the 127 patients in the parent study, 109 participated in the open-label extension study and were followed for an additional 8 years for a total of up to 10 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Enbrel, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Enbrel following an earlier withdrawal from treatment; and 45 (41%) had stopped Enbrel (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire follow-up period. Patients actively taking Enbrel could enter an optional withdrawal-retreatment period once during the extension study based on investigator's judgement of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥ 30% worsening in at least 3 of the 6 ACR Pedi components with ≥ 30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after Enbrel withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the small number of data points, these results should be interpreted with caution.

The safety profile was consistent with that observed in the parent study.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy. Additionally, studies have not been conducted to assess the effects of reducing the recommended dose of Enbrel following its long-term use in patients with JIA.

Paediatric patients with plaque psoriasis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by an sPGA score ≥ 3, involving ≥ 10% of the BSA, and PASI ≥ 12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received Enbrel 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to Enbrel had positive efficacy responses (e.g., PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks

	Enbrel 0.8 mg/kg Once Weekly (N = 106)	**Placebo (N = 105)**
PASI 75, n (%)	60 (57%)[a]	12 (11%)
PASI 50, n (%)	79 (75%)[a]	24 (23%)
sPGA "clear" or "minimal", n (%)	56 (53%)[a]	14 (13%)

Abbreviation: sPGA-static Physician Global Assessment
a. $p < 0.0001$ compared with placebo

After the 12-week double-blind treatment period, all patients received Enbrel 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to Enbrel. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of Enbrel 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with Enbrel was generally comparable to the original 48-week study and did not reveal any new safety findings.

5.2 Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products, as well as the parent compound.

Absorption

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 μg/ml, and the area under the curve was 235 ± 96.6 μg•hr/ml.

Mean serum concentration profiles at steady state in treated RA patients were C_{max} of 2.4 mg/l vs. 2.6 mg/l, C_{min} of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg Enbrel once weekly (n=21) vs. 25 mg Enbrel twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466 μg•hr/ml and 474 μg•hr/ml for 50 mg Enbrel once weekly (N= 154) and 25 mg twice weekly (N = 148), respectively.

Distribution

A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of Enbrel in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.

There is no apparent pharmacokinetic difference between males and females.

Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

Special populations

Renal impairment
Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal failure. The presence of renal impairment should not require a change in dosage.

Hepatic impairment
Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

Elderly
The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
In a polyarticular-course juvenile idiopathic arthritis trial with Enbrel, 69 patients (aged 4 to 17 years) were administered 0.4 mg Enbrel/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Paediatric patients with plaque psoriasis
Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice-weekly.

5.3 Preclinical safety data

In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with Enbrel due to the development of neutralising antibodies in rodents.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Mannitol (E421)
Sucrose
Trometamol

Solvent

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

Chemical and physical in-use stability has been demonstrated for 6 hours at temperatures of up to 25°C after reconstitution. From a microbiological point of view, the reconstituted medicinal product should be used immediately. If not used immediately, storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at temperatures of up to 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Enbrel may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks of removal from refrigeration.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear glass vial (2 ml, type I glass) with rubber stoppers, aluminium seals, and flip-off plastic caps. Enbrel is supplied with pre-filled syringes containing water for injection. The syringes are type I glass. The syringe cover contains dry natural rubber (latex) (see section 4.4). Cartons contain 4, 8 or 24 vials of Enbrel with 4, 8 or 24 pre-filled solvent syringes, 4, 8 or 24 needles, 4, 8 or 24 vial adaptors and 8, 16 or 48 alcohol swabs. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

Enbrel is reconstituted with 1 ml water for injections before use, and administered by subcutaneous injection. Enbrel contains no antibacterial preservative, and therefore, solutions prepared with water for injections should be administered as soon as possible and within 6 hours following reconstitution. The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes or

particles. Some white foam may remain in the vial – this is normal. Enbrel should not be used if all the powder in the vial is not dissolved within 10 minutes. If this is the case, start again with another vial.

Comprehensive instructions for the preparation and administration of the reconstituted Enbrel vial are given in the package leaflet, section 7, "Instructions for use."

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/003
EU/1/99/126/004
EU/1/99/126/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2000
Date of last renewal: 26 November 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg solution for injection in pre-filled syringe
Enbrel 50 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Enbrel 25 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 25 mg of etanercept.

Enbrel 50 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 50 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear, and colourless to pale yellow or pale brown.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Enbrel in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Enbrel can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Enbrel, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis (AS)
Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis
Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

4.2 Posology and method of administration

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients treated with Enbrel should be given the Patient Card.

Enbrel is available in strengths of 10, 25 and 50 mg.

Posology

Rheumatoid arthritis
25 mg Enbrel administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis
The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque psoriasis
The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Special populations

Renal and hepatic impairment
No dose adjustment is required.

Elderly
No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

Paediatric population
The dosage of Enbrel is based on body weight for paediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using the powder and solvent for solution for injection presentations or the powder for solution for injection presentations (see below for dosing for specific indications). Patients weighing 62.5 kg or more, may be dosed using a fixed-dose pre-filled syringe or pre-filled pen.

The safety and efficacy of Enbrel in children aged less than 2 years has not been established.
No data are available.

Juvenile idiopathic arthritis
The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose) given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.

The 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of Enbrel in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age 6 years and above)
The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of Enbrel in children aged below 6 years in the indication plaque psoriasis.

Method of administration

Enbrel is administered by subcutaneous injection (see section 6.6).

Comprehensive instructions for administration are given in the package leaflet, section 7, "Instructions for use." Detailed instructions on unintentional dosing or scheduling variations, including missed doses, are provided in section 3 of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with Enbrel should not be initiated in patients with active infections, including chronic or localised infections.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the brand name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections

Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of Enbrel (see section 4.8). These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. The safety and efficacy of Enbrel in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

Tuberculosis

Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with Enbrel.

Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the Patient Card. Prescribers are reminded of the risk of

false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Enbrel therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including Enbrel, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with Enbrel. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Enbrel in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, Enbrel should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving Enbrel. Enbrel should be used with caution in patients with a history of hepatitis C.

Concurrent treatment with anakinra

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of Enbrel and anakinra is not recommended (see sections 4.5 and 4.8).

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

Allergic reactions

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated.

The needle cover of the pre-filled syringe contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled by, or when Enbrel is administered to, persons with known or possible latex sensitivity.

Immunosuppression

The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of Enbrel in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Enbrel, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Skin cancers
Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving Enbrel compared with control patients, particularly in patients with psoriasis.

Vaccinations

Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. In a double-blind, placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic

arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving Enbrel. The clinical significance of this is unknown.

Autoantibody formation

Treatment with Enbrel may result in the formation of autoimmune antibodies (see section 4.8).

Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data

from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment.

Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, Enbrel was not efficacious, and the mortality rate in patients treated with Enbrel was significantly higher after 6 months. Consequently, Enbrel should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Enbrel in patients who also have moderate to severe alcoholic hepatitis.

Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener's granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener's granulomatosis.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Special populations

Elderly
In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received Enbrel were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Paediatric population

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy (see Vaccinations, above).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with anakinra

Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data).

In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel (see sections 4.4 and 4.8). The

combination Enbrel and anakinra has not demonstrated increased clinical benefit, and is therefore not recommended.

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

Concurrent treatment with sulfasalazine

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

Non-interactions

In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy.

Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Enbrel should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Enbrel during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother’s last dose of Enbrel is generally not recommended.

Breast-feeding

In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Limited information from the published literature indicates etanercept has been detected at low levels in human milk. Etanercept could be considered for use during breast-feeding taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

While systemic exposure in a breastfed infant is expected to be low because etanercept is largely degraded in the gastrointestinal tract, limited data regarding systemic exposure in the breastfed infant are available. Therefore, the administration of live vaccines (e.g., BCG) to a breastfed infant when the mother is receiving etanercept could be considered 16 weeks after stopping breast-feeding (or at an earlier timepoint if the infant etanercept serum levels are undetectable).

Fertility

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

4.7 Effects on ability to drive and use machines

Enbrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), headache, allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for Enbrel. TNF-antagonists, such as Enbrel, affect the immune system and their use may affect the body’s defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with Enbrel. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of Enbrel, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with Enbrel use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Very Rare < 1/10,000**	**Not Known (Cannot be Estimated from Available Data)**
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)*		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic infection)*	Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*		Hepatitis B reactivation, listeria
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers* (see section 4.4)	Malignant melanoma (see section 4.4), lymphoma, leukaemia		Merkel cell carcinoma (see section 4.4), Kaposi's sarcoma
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia*	Aplastic anaemia*	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders		Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*	Vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis)	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis		Worsening of symptoms of dermatomyositis
Nervous system disorders	Headache			CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive (see section 4.4)	New onset cardiac failure congestive (see section 4.4)		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*		
Gastrointestinal disorders			Inflammatory bowel disease			
Hepatobiliary disorders			Elevated liver enzymes*	Autoimmune hepatitis*		

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash	Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions	Toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome		
Renal and urinary disorders				Glomerulonephritis		
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*	Pyrexia				

*see Description of selected adverse reactions, below.

Description of selected adverse reactions

Malignancies and lymphoproliferative disorders
One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. In a group of 2,711 plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

Injection site reactions
Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most

recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with Enbrel developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Serious infections
In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, *Streptococcal* fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Enbrel treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with Enbrel, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received Enbrel. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida, Pneumocystis, Aspergillus,* and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

Autoantibodies
Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

Pancytopenia and aplastic anaemia
There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

Interstitial lung disease
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Concurrent treatment with anakinra
In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

Elevated liver enzymes
In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

Autoimmune hepatitis
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients

were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

Undesirable effects in paediatric patients with plaque psoriasis
In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Enbrel subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Enbrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells, including T-cells, leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etanercept, possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, two studies in adults with non-radiographic axial spondyloarthritis, four studies in adults with plaque psoriasis, three studies in juvenile idiopathic arthritis and one study in paediatric patients with plaque psoriasis.

Adult patients with rheumatoid arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively: ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; $p<0.01$ Enbrel vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Enbrel was significantly better than placebo in all components of the ACR criteria, as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with Enbrel compared to controls at 3 and 6 months.

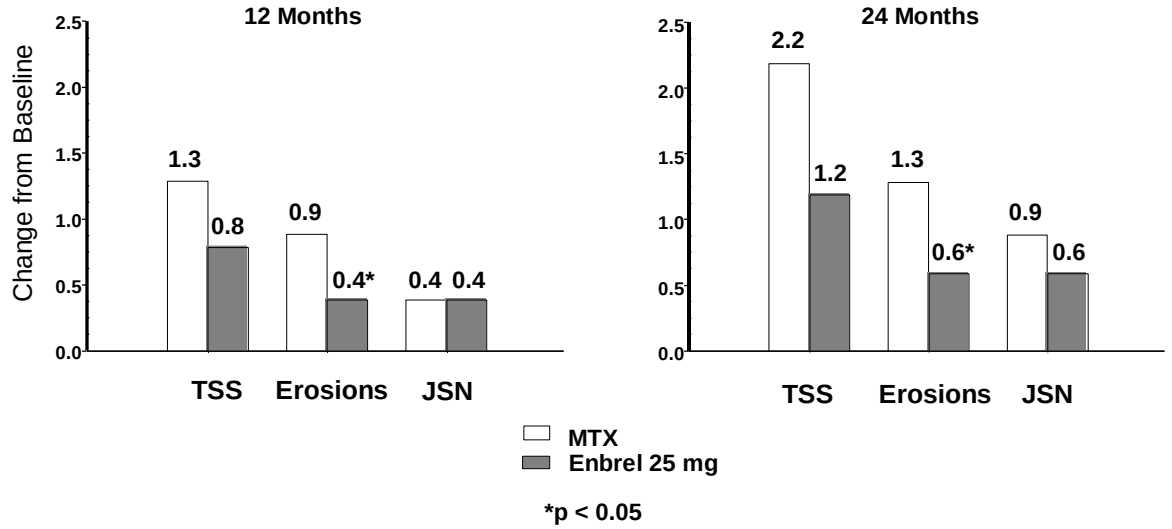
After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received Enbrel without interruption.

The efficacy of Enbrel was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Enbrel were administered subcutaneously (SC) twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement, including onset of action within 2 weeks with Enbrel 25 mg, was similar to that seen in the previous trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44%

of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

Radiographic Progression: Comparison of Enbrel vs. Methotrexate in Patients with RA of <3 Years Duration



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months.

Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
ACR Responses[a]			
ACR 20	58.8%	65.5%	74.5% †,ϕ
ACR 50	36.4%	43.0%	63.2% †,ϕ
ACR 70	16.7%	22.0%	39.8% †,ϕ

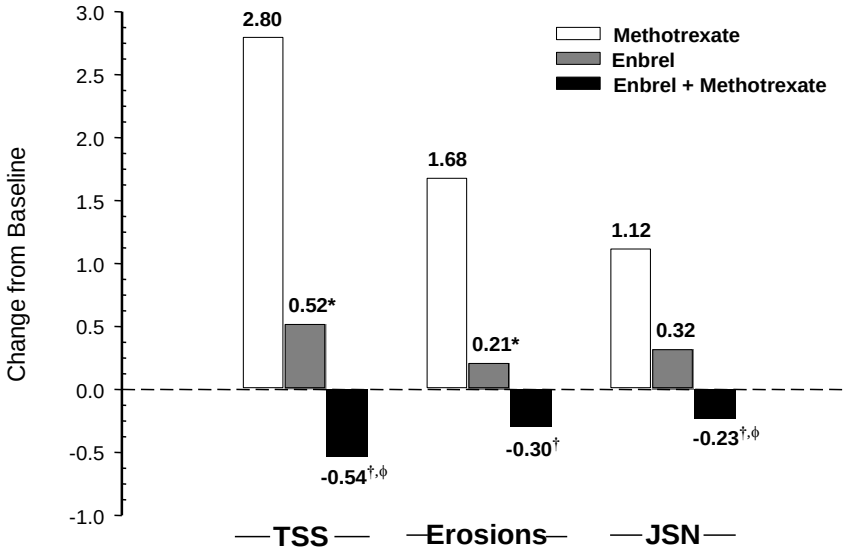
Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
DAS			
Baseline score[b]	5.5	5.7	5.5
Week 52 score[b]	3.0	3.0	2.3†,ϕ
Remission[c]	14%	18%	37%†,ϕ
HAQ			
Baseline	1.7	1.7	1.8
Week 52	1.1	1.0	0.8†,ϕ

a: Patients who did not complete 12 months in the study were considered to be non-responders.
b: Values for Disease Activity Score (DAS) are means.
c: Remission is defined as DAS <1.6.
Pairwise comparison p-values: † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. Enbrel.

Radiographic progression at 12 months was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

Radiographic Progression: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of Enbrel vs. methotrexate, † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. Enbrel.

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p < 0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p < 0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens.

Adult patients with psoriatic arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients had previously been treated with NSAIDs (86%), DMARDs (80%), and corticosteroids (24%). Patients currently on methotrexate therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week methotrexate. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

Clinical responses were expressed as percentages of patients achieving the ACR 20, 50, and 70 response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table below.

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

	Percent of Patients	
	Placebo	Enbrel[a]
Psoriatic Arthritis Response	n = 104	n = 101
ACR 20		
Month 3	15	59[b]
Month 6	13	50[b]
ACR 50		
Month 3	4	38[b]
Month 6	4	37[b]
ACR 70		
Month 3	0	11[b]
Month 6	1	9[c]
PsARC		
Month 3	31	72[b]
Month 6	23	70[b]

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

	Percent of Patients	
	Placebo	Enbrel[a]
Psoriatic Arthritis Response	n = 104	n = 101

a: 25 mg Enbrel SC twice weekly
b: $p < 0.001$, Enbrel vs. placebo
c: $p < 0.01$, Enbrel vs. placebo

Among patients with psoriatic arthritis who received Enbrel, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Enbrel was significantly better than placebo in all measures of disease activity ($p < 0.001$), and responses were similar with and without concomitant methotrexate therapy. Quality of life in psoriatic arthritis patients was assessed at every timepoint using the disability index of the HAQ. The disability index score was significantly improved at all timepoints in psoriatic arthritis patients treated with Enbrel, relative to placebo ($p < 0.001$).

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in the table below. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 12 months was higher in the Enbrel group compared with the placebo group (73% vs. 47%, respectively, $p \leq 0.001$). The effect of Enbrel on radiographic progression was maintained in patients who continued on treatment during the second year. The slowing of peripheral joint damage was observed in patients with polyarticular symmetrical joint involvement.

Mean (SE) Annualized Change from Baseline in Total Sharp Score

Time	Placebo (n = 104)	Etanercept (n = 101)
Month 12	1.00 (0.29)	-0.03 (0.09)[a]

SE = standard error.
a. $p = 0.0001$.

Enbrel treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of Enbrel in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.

No study has been performed in patients with psoriatic arthritis using the 50 mg once-weekly dosing regimen. Evidence of efficacy for the once-weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

Adult patients with ankylosing spondylitis
The efficacy of Enbrel in ankylosing spondylitis was assessed in 3 randomised, double-blind studies comparing twice-weekly administration of 25 mg Enbrel with placebo. A total of 401 patients were enrolled, from which 203 were treated with Enbrel. The largest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of Enbrel (based on dose-finding studies in patients

with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months in 138 patients.

The primary measure of efficacy (ASAS 20) was a ≥20% improvement in at least 3 of the 4 Assessment in Ankylosing Spondylitis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and absence of deterioration in the remaining domain. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% improvement, respectively.

Compared to placebo, treatment with Enbrel resulted in significant improvements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of therapy.

Responses of Patients with Ankylosing Spondylitis in a Placebo-controlled Trial

	Percent of Patients	
Ankylosing Spondylitis Response	Placebo N = 139	Enbrel N = 138
ASAS 20		
2 weeks	22	46[a]
3 months	27	60[a]
6 months	23	58[a]
ASAS 50		
2 weeks	7	24[a]
3 months	13	45[a]
6 months	10	42[a]
ASAS 70		
2 weeks	2	12[b]
3 months	7	29[b]
6 months	5	28[b]
a: p <0.001, Enbrel vs. placebo		
b: p = 0.002, Enbrel vs. placebo		

Among patients with ankylosing spondylitis who received Enbrel, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly vs. 25 mg Enbrel administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once-weekly and 25 mg twice-weekly regimens were similar.

Adult patients with non-radiographic axial spondyloarthritis

Study 1
The efficacy of Enbrel in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received Enbrel 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining

domain. The double-blind period was followed by an open-label period during which all patients receive Enbrel 50 mg weekly for up to an additional 92 weeks. MRIs of the sacroiliac joint and spine were obtained to assess inflammation at baseline and at weeks 12 and 104.

Compared to placebo, treatment with Enbrel resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

Efficacy Response in Placebo-Controlled nr-AxSpa Study: Percent of Patients Achieving Endpoints

Double-Blind Clinical Responses at Week 12	Placebo N=106 to 109*	Enbrel N=103 to 105*
ASAS** 40	15.7	32.4[b]
ASAS 20	36.1	52.4[c]
ASAS 5/6	10.4	33.0[a]
ASAS partial remission	11.9	24.8[c]
BASDAI***50	23.9	43.8[b]

*Some patients did not provide complete data for each endpoint
**ASAS=Assessments in Spondyloarthritis International Society
***Bath Ankylosing Spondylitis Disease Activity Index
a: p <0.001, b:<0.01 and c:<0.05, respectively between Enbrel and placebo

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint (SIJ) as measured by MRI for patients receiving Enbrel. Adjusted mean change from baseline was 3.8 for Enbrel treated (n=95) versus 0.8 for placebo treated (n=105) patients (p<0.001). At week 104, the mean change from baseline in the SPARCC score measured on MRI for all Enbrel-treated subjects was 4.64 for the SIJ (n=153) and 1.40 the spine (n=154).

Enbrel showed statistically significantly greater improvement from baseline to week 12 compared to placebo in most health-related quality of life and physical function assessments, including BASFI (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D Overall Health State Score and SF-36 Physical Component Score.

Clinical responses among nr-AxSpa patients who received Enbrel were apparent at the time of the first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings. At week 104, 8 subjects had progressed to a score of bilateral Grade 2 on spinal X-ray according to the modified New York Radiological Grade, indicative of axial spondyloarthropathy.

Study 2
This multi-center, open-label, phase 4, 3-period study evaluated the withdrawal and retreatment of Enbrel in patients with active nr-AxSpa who achieved an adequate response (inactive disease defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP) less than 1.3) following 24 weeks of treatment.

209 adult patients with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the Assessment of SpondyloArthritis International Society (ASAS) classification criteria of axial spondyloarthritis (but not meeting the modified New York criteria for AS), having positive MRI findings (active inflammation on MRI highly suggestive of sacroiliitis associated with SpA) and/or positive hsCRP (defined as high sensitivity C-reactive protein [hsCRP] >3 mg/l), and active symptoms defined by an ASDAS CRP greater than or equal to 2.1 at the screening visit received open-label Enbrel 50 mg weekly plus stable background NSAID at the optimal tolerated anti-inflammatory dosage for 24 weeks in Period 1. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. At week 24, 119 (57%) patients achieved inactive disease and

entered into the Period 2 40-week withdrawal phase where subjects discontinued etanercept, yet maintained the background NSAID. The primary measure of efficacy was the occurrence of flare (defined as an ASDAS erythrocyte sedimentation rate (ESR) greater than or equal to 2.1) within 40 weeks following withdrawal of Enbrel. Patients who flared were retreated with Enbrel 50 mg weekly for 12 weeks (Period 3).

In Period 2, the proportion of patients experiencing ≥1 flare increased from 22% (25/112) at week 4 to 67% (77/115) at week 40. Overall, 75% (86/115) patients experienced a flare at any time point within 40 weeks following withdrawal of Enbrel.

The key secondary objective of Study 2 was to estimate time to flare after withdrawal of Enbrel and additionally compare the time to flare to patients from Study 1 who met the Study 2 withdrawal phase entry requirements and continued Enbrel therapy.

The median time to flare following withdrawal of Enbrel was 16 weeks (95% CI: 13-24 weeks). Less than 25% of patients in Study 1 who did not have treatment withdrawn experienced a flare over the equivalent 40-weeks as in Period 2 Study 2. The time to flare was statistically significantly shorter in subjects who discontinued Enbrel treatment (Study 2) compared to subjects who received continuous etanercept treatment (Study 1), $p<0.0001$.

Of the 87 patients who entered Period 3 and were retreated with Enbrel 50 mg weekly for 12 weeks, 62% (54/87) reachieved inactive disease, with 50% of them reachieving it within 5 weeks (95% CI: 4-8 weeks).

Adult patients with plaque psoriasis
Enbrel is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least one of the three major systemic therapies as available.

The efficacy of Enbrel versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing Enbrel with other systemic therapies. Instead, the safety and efficacy of Enbrel were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

Study 1 was a Phase 2 study in patients with active, but clinically stable, plaque psoriasis involving ≥ 10% of the body surface area who were ≥ 18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of Enbrel (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. Enbrel was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three Enbrel doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded Enbrel (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg Enbrel, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg Enbrel twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg Enbrel or placebo once weekly for 12 weeks and then all patients received open-label 50 mg Enbrel once weekly for an additional 12 weeks.

In study 1, the Enbrel-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) ($p < 0.0001$). At 24 weeks, 56% of patients in the Enbrel-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

Responses of Patients with Psoriasis in Studies 2, 3 and 4

	Study 2					Study 3			Study 4		
		----------Enbrel---------					--------Enbrel-------			-------Enbrel------	
		25 mg BIW		50 mg BIW			25 mg BIW	50 mg BIW		50 mg QW	50 mg QW
Response (%)	Placebo n = 166 wk 12	n = 162 wk 12	n = 162 wk 24[a]	n = 164 wk 12	n = 164 wk 24[a]	Placebo n = 193 wk 12	n = 196 wk 12	n = 196 wk 12	Placebo n = 46 wk 12	n = 96 wk 12	n = 90 wk 24[a]
PASI 50	14	58*	70	74*	77	9	64*	77*	9	69*	83
PASI 75	4	34*	44	49*	59	3	34*	49*	2	38*	71
DSGA[b], clear or almost clear	5	34*	39	49*	55	4	39*	57*	4	39*	64

*$p \leq 0.0001$ compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving Enbrel 25 mg BIW or 50 mg once weekly from week 13 to week 24.

b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received Enbrel, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥ 150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned, with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with Enbrel in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Enbrel dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the Enbrel-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) ($p< 0.0001$). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where Enbrel was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

Antibodies to Enbrel
Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
The safety and efficacy of Enbrel were assessed in a two-part study in 69 children with polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic onset). Patients aged 4 to 17 years with moderately to severely active polyarticular-course juvenile idiopathic arthritis refractory to, or intolerant of, methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomised to remain on Enbrel or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥ 30% worsening in three of six JRA core set criteria and ≥ 30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive Enbrel for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

Long-term safety of Enbrel monotherapy (n=103), Enbrel plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study (n=127), 60 patients with extended oligoarthritis (EO) (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with Enbrel at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Of the 127 patients in the parent study, 109 participated in the open-label extension study and were followed for an additional 8 years for a total of up to 10 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Enbrel, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Enbrel following an earlier withdrawal from treatment; and 45 (41%) had stopped Enbrel (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire follow-up period. Patients actively taking Enbrel could enter an optional withdrawal-retreatment period once during the extension study based on investigator's judgement of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥ 30% worsening in at least 3 of the 6 ACR Pedi components with ≥ 30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after Enbrel withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the small number of data points, these results should be interpreted with caution.

The safety profile was consistent with that observed in the parent study.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy. Additionally, studies have not been conducted to assess the effects of reducing the recommended dose of Enbrel following its long-term use in patients with JIA.

Paediatric patients with plaque psoriasis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by an sPGA score ≥ 3, involving ≥ 10% of the BSA, and PASI ≥ 12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received Enbrel 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to Enbrel had positive efficacy responses (e.g., PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks

	Enbrel 0.8 mg/kg Once Weekly (N = 106)	**Placebo (N = 105)**
PASI 75, n (%)	60 (57%)[a]	12 (11%)
PASI 50, n (%)	79 (75%)[a]	24 (23%)
sPGA "clear" or "minimal", n (%)	56 (53%)[a]	14 (13%)

Abbreviation: sPGA-static Physician Global Assessment
a. $p < 0.0001$ compared with placebo

After the 12-week double-blind treatment period, all patients received Enbrel 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to Enbrel. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of Enbrel 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with Enbrel was generally comparable to the original 48-week study and did not reveal any new safety findings.

5.2 Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products, as well as the parent compound.

Absorption

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 μg/ml, and the area under the curve was 235 ± 96.6 μg•hr/ml.

Mean serum concentration profiles at steady state in treated RA patients were C_{max} of 2.4 mg/l vs. 2.6 mg/l, C_{min} of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg Enbrel once weekly (n=21) vs. 25 mg Enbrel twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466 μg•hr/ml and 474 μg•hr/ml for 50 mg Enbrel once weekly (N = 154) and 25 mg twice weekly (N = 148), respectively.

Distribution

A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of Enbrel in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.

There is no apparent pharmacokinetic difference between males and females.

Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

Special populations

Renal impairment
Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal failure. The presence of renal impairment should not require a change in dosage.

Hepatic impairment
Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

Elderly
The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
In a polyarticular-course juvenile idiopathic arthritis trial with Enbrel, 69 patients (aged 4 to 17 years) were administered 0.4 mg Enbrel/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Paediatric patients with plaque psoriasis
Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice-weekly.

5.3 Preclinical safety data

In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with Enbrel due to the development of neutralising antibodies in rodents.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium chloride
L-Arginine hydrochloride
Sodium phosphate monobasic dihydrate
Sodium phosphate dibasic dihydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.

Enbrel may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks of removal from refrigeration.

Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Enbrel 25 mg solution for injection in pre-filled syringe

Clear glass syringe (type I glass) with stainless steel needle, rubber needle cover and plastic plunger. Cartons contain 4, 8, 12 or 24 pre-filled syringes of Enbrel and 4, 8, 12 or 24 alcohol swabs. The needle cover contains dry natural rubber (latex) (see section 4.4). Not all pack sizes may be marketed.

Enbrel 50 mg solution for injection in pre-filled syringe

Clear glass syringe (type I glass) with stainless steel needle, rubber needle cover and plastic plunger. Cartons contain 2, 4 or 12 pre-filled syringes of Enbrel with 2, 4 or 12 alcohol swabs. The needle cover contains dry natural rubber (latex) (see section 4.4). Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before injection, Enbrel single-use pre-filled syringe should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled syringe to reach room temperature. The solution should be clear to slightly opalescent, colourless to pale yellow or pale brown and may contain small translucent or white particles of protein.

Comprehensive instructions for administration are given in the package leaflet, section 7, "Instructions for use."

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Enbrel 25 mg solution for injection in pre-filled syringe

EU/1/99/126/013
EU/1/99/126/014
EU/1/99/126/015
EU/1/99/126/026

Enbrel 50 mg solution for injection in pre-filled syringe

EU/1/99/126/016
EU/1/99/126/017
EU/1/99/126/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2000
Date of last renewal: 26 November 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg solution for injection in pre-filled pen
Enbrel 50 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Enbrel 25 mg solution for injection in pre-filled pen

Each pre-filled pen contains 25 mg of etanercept.

Enbrel 50 mg solution for injection in pre-filled pen

Each pre-filled pen contains 50 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear, and colourless to pale yellow or pale brown.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Enbrel in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Enbrel can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Enbrel, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis (AS)
Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis
Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

4.2 Posology and method of administration

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients treated with Enbrel should be given the Patient Card.

The Enbrel pre-filled pen is available in 25 mg and 50 mg strengths. Other presentations of Enbrel are available in strengths of 10 mg, 25 mg, and 50 mg.

Posology

Rheumatoid arthritis
25 mg Enbrel administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis
The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque psoriasis
The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Special populations

Renal and hepatic impairment
No dose adjustment is required.

Elderly
No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

Paediatric population
The dosage of Enbrel is based on body weight for paediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using the powder and solvent for solution for injection presentations or the powder for solution for injection presentations (see below for dosing for specific indication). Patients weighing 62.5 kg or more, may be dosed using a fixed-dose pre-filled syringe or pre-filled pen.

The safety and efficacy of Enbrel in children aged less than 2 years has not been established.
No data are available.

Juvenile idiopathic arthritis
The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.

The 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of Enbrel in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age 6 years and above)
The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of Enbrel in children aged below 6 years in the indication plaque psoriasis.

Method of administration

Enbrel is administered by subcutaneous injection (see section 6.6).

Comprehensive instructions for administration are given in the package leaflet, section 7, "Instructions for use." Detailed instructions on unintentional dosing or scheduling variations, including missed doses, are provided in section 3 of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with Enbrel should not be initiated in patients with active infections including chronic or localised infections.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the brand name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections

Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of Enbrel (see section 4.8). These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. The safety and efficacy of Enbrel in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections such as advanced or poorly controlled diabetes.

Tuberculosis

Cases of active tuberculosis including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported in patients treated with Enbrel.

Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray,

should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the Patient Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Enbrel therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including Enbrel, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with Enbrel. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Enbrel in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, Enbrel should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving Enbrel. Enbrel should be used with caution in patients with a history of hepatitis C.

Concurrent treatment with anakinra

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus the combined use of Enbrel and anakinra is not recommended (see sections 4.5 and 4.8).

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

Allergic reactions

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated.

The needle cap of the pre-filled pen contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled by or when Enbrel is administered to persons with known or possible latex sensitivity.

Immunosuppression

The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of Enbrel in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Enbrel, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Skin cancers
Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving Enbrel compared with control patients, particularly in patients with psoriasis.

Vaccinations

Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. In a double blind, placebo controlled, randomised clinical study in adult patients with psoriatic arthritis 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study most psoriatic arthritis

patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower and few patients had two-fold rises in titres compared to patients not receiving Enbrel. The clinical significance of this is unknown.

Autoantibody formation

Treatment with Enbrel may result in the formation of autoimmune antibodies (see section 4.8).

Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data

from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment.

Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, Enbrel was not efficacious, and the mortality rate in patients treated with Enbrel was significantly higher after 6 months. Consequently, Enbrel should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Enbrel in patients who also have moderate to severe alcoholic hepatitis.

Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener's granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener's granulomatosis.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Special populations

Elderly
In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received Enbrel were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Paediatric population

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy (see Vaccinations, above).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with anakinra

Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data).

In addition, in a double-blind placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel (see sections 4.4 and 4.8). The

combination Enbrel and anakinra has not demonstrated increased clinical benefit and is therefore not recommended.

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

Concurrent treatment with sulfasalazine

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

Non-interactions

In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy.

Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Enbrel should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Enbrel during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother’s last dose of Enbrel is generally not recommended.

Breast-feeding

In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Limited information from the published literature indicates etanercept has been detected at low levels in human milk. Etanercept could be considered for use during breast-feeding taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

While systemic exposure in a breastfed infant is expected to be low because etanercept is largely degraded in the gastrointestinal tract, limited data regarding systemic exposure in the breastfed infant are available. Therefore, the administration of live vaccines (e.g., BCG) to a breastfed infant when the mother is receiving etanercept could be considered 16 weeks after stopping breast-feeding (or at an earlier timepoint if the infant etanercept serum levels are undetectable).

Fertility

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

4.7 Effects on ability to drive and use machines

Enbrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), headache, allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for Enbrel. TNF-antagonists, such as Enbrel, affect the immune system and their use may affect the body’s defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with Enbrel. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of Enbrel, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with Enbrel use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)*		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic infection)*	Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*		Hepatitis B reactivation, listeria
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers* (see section 4.4)	Malignant melanoma (see section 4.4), lymphoma, leukaemia		Merkel cell carcinoma (see section 4.4), Kaposi's sarcoma
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia*	Aplastic anaemia*	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders		Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*	Vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis)	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis		Worsening of symptoms of dermatomyositis
Nervous system disorders	Headache			CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive (see section 4.4)	New onset cardiac failure congestive (see section 4.4)		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*		

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
Gastrointestinal disorders			Inflammatory bowel disease			
Hepatobiliary disorders			Elevated liver enzymes*	Autoimmune hepatitis*		
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash	Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions	Toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome		
Renal and urinary disorders				Glomerulonephritis		
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*	Pyrexia				

*see Description of selected adverse reactions, below.

Description of selected adverse reactions

Malignancies and lymphoproliferative disorders
One hundred and twenty-nine new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. In a group of 2,711 plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

Injection site reactions
Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first

month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with Enbrel developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Serious infections
In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, Streptococcal fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Enbrel treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with Enbrel, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received Enbrel. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida, Pneumocystis*, *Aspergillus*, and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

Autoantibodies
Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥ 1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel

compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

Pancytopenia and aplastic anaemia
There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

Interstitial lung disease
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Concurrent treatment with anakinra
In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

Elevated liver enzymes
In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

Autoimmune hepatitis
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

Undesirable effects in paediatric patients with plaque psoriasis
In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Enbrel subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Enbrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells including T-cells leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF-binding to its cell surface receptors and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors such as etanercept possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, two studies in adults with non-radiographic axial spondyloarthritis, four studies in adults with plaque psoriasis, three studies in juvenile idiopathic arthritis and one study in paediatric patients with plaque psoriasis.

Adult patients with rheumatoid arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months respectively: ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; $p < 0.01$ Enbrel vs placebo at all timepoints for both ACR 20 and ACR 50 responses).

Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Enbrel was significantly better than placebo in all components of the ACR criteria as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with Enbrel compared to controls at 3 and 6 months.

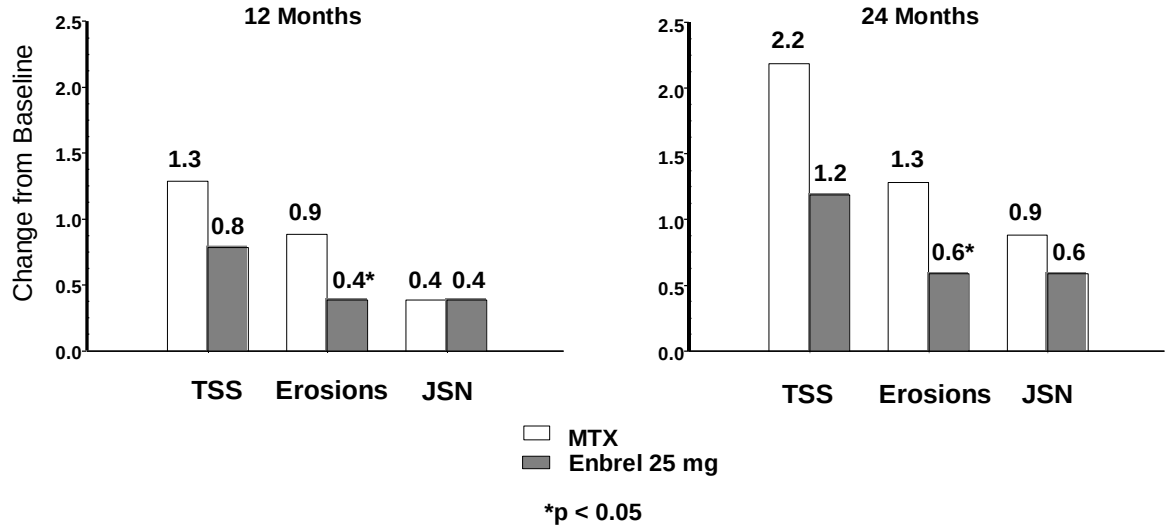
After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received Enbrel without interruption.

The efficacy of Enbrel was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Enbrel were administered SC twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement including onset of action within 2 weeks with Enbrel 25 mg was similar to that seen in the previous trials, and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44% of

patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

Radiographic Progression: Comparison of Enbrel vs Methotrexate in Patients with RA of <3 Years Duration



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and of the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months.

Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs Methotrexate vs Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
ACR Responses[a]			
ACR 20	58.8%	65.5%	74.5% †,ϕ
ACR 50	36.4%	43.0%	63.2% †,ϕ
ACR 70	16.7%	22.0%	39.8% †,ϕ

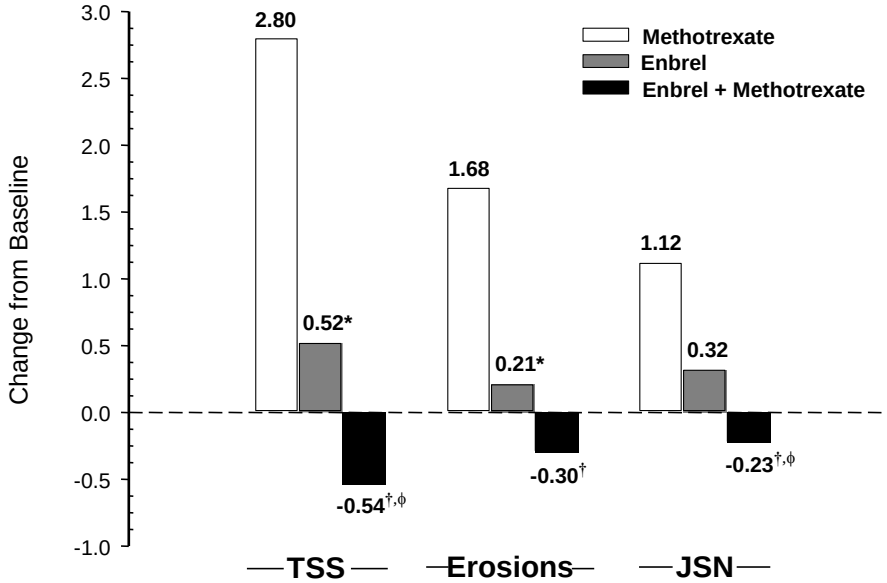
Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs Methotrexate vs Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
DAS			
Baseline score[b]	5.5	5.7	5.5
Week 52 score[b]	3.0	3.0	2.3†,ϕ
Remission[c]	14%	18%	37%†,ϕ
HAQ			
Baseline	1.7	1.7	1.8
Week 52	1.1	1.0	0.8†,ϕ

a: Patients who did not complete 12 months in the study were considered to be non-responders.
b: Values for Disease Activity Score (DAS) are means.
c: Remission is defined as DAS <1.6
Pairwise comparison p-values: † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs Enbrel

Radiographic progression at 12 months was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

Radiographic Progression: Comparison of Enbrel vs Methotrexate vs Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of Enbrel vs methotrexate, † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs Enbrel

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p < 0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p < 0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens. A single 50 mg/ml injection of Enbrel was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

Adult patients with psoriatic arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients had previously been treated with NSAIDs (86%), DMARDs (80%), and corticosteroids (24%). Patients currently on methotrexate therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week methotrexate. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

Clinical responses were expressed as percentages of patients achieving the ACR 20, 50, and 70 response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table below.

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

	Percent of Patients	
	Placebo	Enbrel[a]
Psoriatic Arthritis Response	n = 104	n = 101
ACR 20		
Month 3	15	59[b]
Month 6	13	50[b]
ACR 50		
Month 3	4	38[b]
Month 6	4	37[b]
ACR 70		
Month 3	0	11[b]
Month 6	1	9[c]
PsARC		
Month 3	31	72[b]
Month 6	23	70[b]

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

	Percent of Patients	
	Placebo	Enbrel[a]
Psoriatic Arthritis Response	n = 104	n = 101

a: 25 mg Enbrel SC twice weekly
b: $p < 0.001$, Enbrel vs. placebo
c: $p < 0.01$, Enbrel vs. placebo

Among patients with psoriatic arthritis who received Enbrel, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Enbrel was significantly better than placebo in all measures of disease activity ($p < 0.001$), and responses were similar with and without concomitant methotrexate therapy. Quality of life in psoriatic arthritis patients was assessed at every timepoint using the disability index of the HAQ. The disability index score was significantly improved at all timepoints in psoriatic arthritis patients treated with Enbrel, relative to placebo ($p < 0.001$).

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in the Table below. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 12 months was higher in the Enbrel group compared with the placebo group (73% vs. 47%, respectively, $p \leq 0.001$). The effect of Enbrel on radiographic progression was maintained in patients who continued on treatment during the second year. The slowing of peripheral joint damage was observed in patients with polyarticular symmetrical joint involvement.

Mean (SE) Annualized Change from Baseline in Total Sharp Score

Time	Placebo (n = 104)	Etanercept (n = 101)
Month 12	1.00 (0.29)	-0.03 (0.09)[a]

SE = standard error.
a. $p = 0.0001$.

Enbrel treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of Enbrel in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.
No study has been performed in patients with psoriatic arthritis using the 50 mg once weekly dosing regimen. Evidence of efficacy for the once weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

Adult patients with ankylosing spondylitis
The efficacy of Enbrel in ankylosing spondylitis was assessed in 3 randomised, double-blind studies comparing twice weekly administration of 25 mg Enbrel with placebo. A total of 401 patients were enrolled from which 203 were treated with Enbrel. The largest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of Enbrel (based on dose-finding studies in patients

with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months in 138 patients.

The primary measure of efficacy (ASAS 20) was a ≥ 20% improvement in at least 3 of the 4 Assessment in Ankylosing Spondylitis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and absence of deterioration in the remaining domain. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% improvement, respectively.

Compared to placebo, treatment with Enbrel resulted in significant improvements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of therapy.

Responses of Patients with Ankylosing Spondylitis in a Placebo-Controlled Trial

	Percent of Patients	
Ankylosing Spondylitis Response	Placebo N = 139	Enbrel N = 138
ASAS 20		
2 weeks	22	46[a]
3 months	27	60[a]
6 months	23	58[a]
ASAS 50		
2 weeks	7	24[a]
3 months	13	45[a]
6 months	10	42[a]
ASAS 70:		
2 weeks	2	12[b]
3 months	7	29[b]
6 months	5	28[b]
a: p <0.001, Enbrel vs. Placebo		
b: p = 0.002, Enbrel vs. placebo		

Among patients with ankylosing spondylitis who received Enbrel, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly vs 25 mg Enbrel administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once weekly and 25 mg twice weekly regimens were similar.

Adult patients with non-radiographic axial spondyloarthritis

Study 1
The efficacy of Enbrel in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received Enbrel 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40%

improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. The double-blind period was followed by an open-label period during which all patients receive Enbrel 50 mg weekly for up to an additional 92 weeks. MRIs of the sacroiliac joint and spine were obtained to assess inflammation at baseline and at weeks 12 and 104.

Compared to placebo, treatment with Enbrel resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

Efficacy Response in Placebo-Controlled nr-AxSpa Study: Percent of Patients Achieving Endpoints

Double-Blind Clinical Responses at Week 12	Placebo N=106 to 109*	Enbrel N=103 to 105*
ASAS** 40	15.7	32.4[b]
ASAS 20	36.1	52.4[c]
ASAS 5/6	10.4	33.0[a]
ASAS partial remission	11.9	24.8[c]
BASDAI***50	23.9	43.8[b]

*Some patients did not provide complete data for each endpoint
**ASAS=Assessments in Spondyloarthritis International Society
***Bath Ankylosing Spondylitis Disease Activity Index
a: p <0.001, b:<0.01 and c:<0.05, respectively between Enbrel and placebo

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint (SIJ) as measured by MRI for patients receiving Enbrel. Adjusted mean change from baseline was 3.8 for Enbrel treated (n=95) versus 0.8 for placebo treated (n=105) patients (p<0.001). At week 104, the mean change from baseline in the SPARCC score measured on MRI for all Enbrel-treated subjects was 4.64 for the SIJ (n=153) and 1.40 the spine (n=154).

Enbrel showed statistically significantly greater improvement from baseline to week 12 compared to placebo in most health-related quality of life and physical function assessments, including BASFI (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D Overall Health State Score and SF-36 Physical Component Score.

Clinical responses among nr-AxSpa patients who received Enbrel were apparent at the time of the first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings. At week 104, 8 subjects had progressed to a score of bilateral Grade 2 on spinal X-ray according to the modified New York Radiological Grade, indicative of axial spondyloarthropathy.

Study 2
This multi-center, open-label, phase 4, 3-period study evaluated the withdrawal and retreatment of Enbrel in patients with active nr-AxSpa who achieved an adequate response (inactive disease defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP) less than 1.3) following 24 weeks of treatment.

209 adult patients with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the Assessment of SpondyloArthritis International Society (ASAS) classification criteria of axial spondyloarthritis (but not meeting the modified New York criteria for AS), having positive MRI findings (active inflammation on MRI highly suggestive of sacroiliitis associated with SpA) and/or positive hsCRP (defined as high sensitivity C-reactive protein [hsCRP] > 3 mg/l), and active symptoms defined by an ASDAS CRP greater than or equal to 2.1 at the screening visit received open-label Enbrel 50 mg weekly plus stable background NSAID at the optimal tolerated anti-inflammatory dosage for 24 weeks in Period 1. Patients were also required to have an inadequate

response or intolerance to two or more NSAIDs. At week 24, 119 (57%) patients achieved inactive disease and entered into the Period 2 40-week withdrawal phase where subjects discontinued etanercept, yet maintained the background NSAID. The primary measure of efficacy was the occurrence of flare (defined as an ASDAS erythrocyte sedimentation rate (ESR) greater than or equal to 2.1) within 40 weeks following withdrawal of Enbrel. Patients who flared were retreated with Enbrel 50 mg weekly for 12 weeks (Period 3).

In Period 2, the proportion of patients experiencing ≥1 flare increased from 22% (25/112) at week 4 to 67% (77/115) at week 40. Overall, 75% (86/115) patients experienced a flare at any time point within 40 weeks following withdrawal of Enbrel.

The key secondary objective of Study 2 was to estimate time to flare after withdrawal of Enbrel and additionally compare the time to flare to patients from Study 1 who met the Study 2 withdrawal phase entry requirements and continued Enbrel therapy.

The median time to flare following withdrawal of Enbrel was 16 weeks (95% CI: 13-24 weeks). Less than 25% of patients in Study 1 who did not have treatment withdrawn experienced a flare over the equivalent 40-weeks as in Period 2 Study 2. The time to flare was statistically significantly shorter in subjects who discontinued Enbrel treatment (Study 2) compared to subjects who received continuous etanercept treatment (Study 1), $p<0.0001$.

Of the 87 patients who entered Period 3 and were retreated with Enbrel 50 mg weekly for 12 weeks, 62% (54/87) reachieved inactive disease, with 50% of them reachieving it within 5 weeks (95% CI: 4-8 weeks).

Adult patients with plaque psoriasis
Enbrel is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI< 50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least one of the three major systemic therapies as available.

The efficacy of Enbrel versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing Enbrel with other systemic therapies. Instead, the safety and efficacy of Enbrel were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

Study 1 was a Phase 2 study in patients with active but clinically stable plaque psoriasis involving ≥ 10% of the body surface area that were ≥ 18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of Enbrel (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. Enbrel was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three Enbrel doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded Enbrel (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg Enbrel, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg Enbrel twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg Enbrel or placebo once weekly for 12 weeks and then all patients received open-label 50 mg Enbrel once weekly for an additional 12 weeks.

In study 1, the Enbrel-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) ($p< 0.0001$). At 24 weeks, 56% of patients in the Enbrel-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

Responses of Patients with Psoriasis in Studies 2, 3 And 4

	----------Study 2----------					----------Study 3----------			----------Study 4----------		
		----------Enbrel---------					--------Enbrel-------			-------Enbrel------	
Response (%)	Placebo n = 166 wk 12	25 mg BIW n = 162 wk 12	25 mg BIW n = 162 wk 24[a]	50 mg BIW n = 164 wk 12	50 mg BIW n = 164 wk 24[a]	Placebo n = 193 wk 12	25 mg BIW n = 196 wk 12	50 mg BIW n = 196 wk 12	Placebo n = 46 wk 12	50 mg QW n = 96 wk 12	50 mg QW n = 90 wk 24[a]
PASI 50	14	58*	70	74*	77	9	64*	77*	9	69*	83
PASI 75	4	34*	44	49*	59	3	34*	49*	2	38*	71
DSGA[b], clear or almost clear	5	34*	39	49*	55	4	39*	57*	4	39*	64

*$p \leq 0.0001$ compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving Enbrel 25 mg BIW or 50 mg once weekly from week 13 to week 24.

b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received Enbrel, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥ 150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with Enbrel in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Enbrel dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the Enbrel-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) ($p<0.0001$). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where Enbrel was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

Antibodies to Enbrel
Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
The safety and efficacy of Enbrel were assessed in a two-part study in 69 children with polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic onset). Patients aged 4 to 17 years with moderately to severely active polyarticular-course juvenile idiopathic arthritis refractory to, or intolerant of, methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomised to remain on Enbrel or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥ 30% worsening in three of six JRA core set criteria and ≥ 30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive Enbrel for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

Long-term safety of Enbrel monotherapy (n=103), Enbrel plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years

with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study (n=127), 60 patients with extended oligoarthritis (EO) (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with Enbrel at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Of the 127 patients in the parent study, 109 participated in the open-label extension study and were followed for an additional 8 years for a total of up to 10 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Enbrel, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Enbrel following an earlier withdrawal from treatment; and 45 (41%) had stopped Enbrel (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire follow-up period. Patients actively taking Enbrel could enter an optional withdrawal-retreatment period once during the extension study based on investigator's judgement of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥ 30% worsening in at least 3 of the 6 ACR Pedi components with ≥ 30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after Enbrel withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the small number of data points, these results should be interpreted with caution.

The safety profile was consistent with that observed in the parent study.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy. Additionally, studies have not been conducted to assess the effects of reducing the recommended dose of Enbrel following its long-term use in patients with JIA.

Paediatric patients with plaque psoriasis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by a sPGA score ≥ 3, involving ≥ 10% of the BSA, and PASI ≥ 12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received Enbrel 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to Enbrel had positive efficacy responses (e.g. PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks

	Enbrel 0.8 mg/kg Once Weekly (N = 106)	**Placebo (N = 105)**
PASI 75, n (%)	60 (57%)[a]	12 (11%)
PASI 50, n (%)	79 (75%)[a]	24 (23%)
sPGA "clear" or "minimal", n (%)	56 (53%)[a]	14 (13%)

Abbreviation: sPGA-static Physician Global Assessment.

a. $p < 0.0001$ compared with placebo.

After the 12-week double-blind treatment period, all patients received Enbrel 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to Enbrel. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of Enbrel 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with Enbrel was generally comparable to the original 48-week study and did not reveal any new safety findings.

5.2 Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products as well as the parent compound.

Absorption

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 μg/ml, and the area under the curve was 235 ± 96.6 μg•hr/ml.

Mean serum concentration profiles at steady state in treated RA patients were C_{max} of 2.4 mg/l vs. 2.6 mg/l, C_{min} of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg Enbrel once weekly (n=21) vs. 25 mg Enbrel twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466 μg•hr/ml and 474 μg•hr/ml for 50 mg Enbrel once weekly (N = 154) and 25 mg twice weekly (N = 148), respectively.

Distribution

A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of Enbrel in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.

There is no apparent pharmacokinetic difference between males and females.

Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

Special populations

Renal impairment
Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal failure. The presence of renal impairment should not require a change in dosage.

Hepatic impairment
Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

Elderly
The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
In a polyarticular-course juvenile idiopathic arthritis trial with Enbrel, 69 patients (aged 4 to 17 years) were administered 0.4 mg Enbrel/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Paediatric patients with plaque psoriasis
Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice weekly.

5.3 Preclinical safety data

In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with Enbrel due to the development of neutralising antibodies in rodents.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium chloride
L-Arginine hydrochloride
Sodium phosphate monobasic dihydrate
Sodium phosphate dibasic dihydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Enbrel may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks of removal from refrigeration.

Keep the pre-filled pens in the outer carton in order to protect from light.

6.5 Nature and contents of container

<u>25 mg solution for injection in pre-filled pen</u>

Pre-filled pen containing a 25 mg pre-filled syringe of Enbrel. The syringe inside the pen is made from clear type 1 glass with a stainless steel 27 gauge needle, rubber needle cover, and plastic plunger. The needle cap of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Cartons contain 4, 8 or 24 pre-filled pens of Enbrel with 4, 8 or 24 alcohol swabs. Not all pack sizes may be marketed.

<u>50 mg solution for injection in pre-filled pen</u>

Pre-filled pen containing a 50 mg pre-filled syringe of Enbrel. The syringe inside the pen is made from clear type 1 glass with a stainless steel 27 gauge needle, rubber needle cover, and plastic plunger. The needle cap of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Cartons contain 2, 4 or 12 pre-filled pens of Enbrel with 2, 4 or 12 alcohol swabs. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

Before injection, Enbrel single-use pre-filled pens should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled pen to reach room temperature. By looking through the inspection window, the solution should be clear to slightly opalescent, colourless to pale yellow or pale brown and may contain small translucent or white particles of protein.

Comprehensive instructions for administration are given in the package leaflet (section 7 "Instructions for use").

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Enbrel 25 mg solution for injection in pre-filled pen
EU/1/99/126/023
EU/1/99/126/024
EU/1/99/126/025

Enbrel 50 mg solution for injection in pre-filled pen
EU/1/99/126/019
EU/1/99/126/020
EU/1/99/126/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2000
Date of last renewal: 26 November 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 10 mg powder and solvent for solution for injection for paediatric use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg of etanercept. When reconstituted, the solution contains 10 mg/ml of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (powder for injection).

The powder is white. The solvent is a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

4.2 Posology and method of administration

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of juvenile idiopathic arthritis or paediatric plaque psoriasis. Patients treated with Enbrel should be given the Patient Card.

Posology

Special populations

Renal and hepatic impairment
No dose adjustment is required.

Paediatric population

The 10 mg presentation is for paediatric patients prescribed a dose of 10 mg or less. Each vial of Enbrel 10 mg should be used on a single occasion in a single patient, and the remainder of the vial should be discarded.

Juvenile idiopathic arthritis
The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose) given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of Enbrel in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age 6 years and above)
The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of Enbrel in children aged below 6 years in the indication plaque psoriasis.

Method of administration

Enbrel is administered by subcutaneous injection. Enbrel powder for solution must be reconstituted in 1 ml of solvent before use (see section 6.6).

Comprehensive instructions for the preparation and administration of the reconstituted Enbrel vial are given in the package leaflet, section 7, "Instructions for use." Detailed instructions on unintentional dosing or scheduling variations, including missed doses, are provided in section 3 of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with Enbrel should not be initiated in patients with active infections, including chronic or localised infections.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the brand name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections

Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of Enbrel (see section 4.8). These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. The safety and efficacy of Enbrel in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

Tuberculosis

Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with Enbrel.

Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the Patient Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Enbrel therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including Enbrel, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with Enbrel. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Enbrel in patients

previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, Enbrel should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving Enbrel. Enbrel should be used with caution in patients with a history of hepatitis C.

Concurrent treatment with anakinra

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of Enbrel and anakinra is not recommended (see sections 4.5 and 4.8).

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

Allergic reactions

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated.

The rubber tip cap (closure) of the diluent syringe contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled by, or when Enbrel is administered to, persons with known or possible latex sensitivity.

Immunosuppression

The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of Enbrel in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Enbrel, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Skin cancers
Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving Enbrel compared with control patients, particularly in patients with psoriasis.

Vaccinations

Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. In a double-blind, placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving Enbrel. The clinical significance of this is unknown.

Autoantibody formation

Treatment with Enbrel may result in the formation of autoimmune antibodies (see section 4.8).

Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

In a controlled clinical trial of two years duration in adult rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment.

Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, Enbrel was not efficacious, and the mortality rate in patients treated with Enbrel was significantly higher after 6 months. Consequently, Enbrel should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Enbrel in patients who also have moderate to severe alcoholic hepatitis.

Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener’s granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener’s granulomatosis.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Special populations

Elderly
In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received Enbrel were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Paediatric population

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy (see Vaccinations, above).

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with anakinra

Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data).

In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel (see sections 4.4 and 4.8). The combination Enbrel and anakinra has not demonstrated increased clinical benefit, and is therefore not recommended.

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

Concurrent treatment with sulfasalazine

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

Non-interactions

In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with

methotrexate, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy.

Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Enbrel should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Enbrel during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother’s last dose of Enbrel is generally not recommended.

Breast-feeding

In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Limited information from the published literature indicates etanercept has been detected at low levels in human milk. Etanercept could be considered for use during breast-feeding taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

While systemic exposure in a breastfed infant is expected to be low because etanercept is largely degraded in the gastrointestinal tract, limited data regarding systemic exposure in the breastfed infant are available. Therefore, the administration of live vaccines (e.g., BCG) to a breastfed infant when the mother is receiving etanercept could be considered 16 weeks after stopping breast-feeding (or at an earlier timepoint if the infant etanercept serum levels are undetectable).

Fertility

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

4.7 Effects on ability to drive and use machines

Enbrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients (see below, Undesirable effects in adults). Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

Undesirable effects in paediatric patients with plaque psoriasis
In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

Adult population

Undesirable effects in adults
The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), headache, allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for Enbrel. TNF-antagonists, such as Enbrel, affect the immune system and their use may affect the body’s defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with Enbrel. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of Enbrel, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with Enbrel use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Very Rare < 1/10,000**	**Not Known (Cannot be Estimated from Available Data)**
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)*		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic infection)*	Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*		Hepatitis B reactivation, listeria
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers* (see section 4.4)	Malignant melanoma (see section 4.4), lymphoma, leukaemia		Merkel cell carcinoma (see section 4.4), Kaposi's sarcoma
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia*	Aplastic anaemia*	Histiocytosis haematophagic (macrophage activation syndrome)†
Immune system disorders		Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*	Vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis)	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis		Worsening of symptoms of dermatomyositis

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
Nervous system disorders	Headache			CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive (see section 4.4)	New onset cardiac failure congestive (see section 4.4)		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*		
Gastrointestinal disorders			Inflammatory bowel disease			
Hepatobiliary disorders			Elevated liver enzymes*	Autoimmune hepatitis*		
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash	Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions	Toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome		
Renal and urinary disorders				Glomerulonephritis		

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*	Pyrexia				

*see Description of selected adverse reactions, below.
†Please see sub-section 'Undesirable effects in paediatric patients with juvenile idiopathic arthritis' above.

Description of selected adverse reactions

Malignancies and lymphoproliferative disorders
One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. In a group of 2,711 plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

Injection site reactions
Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with Enbrel developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Serious infections
In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin

infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, *Streptococcal* fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Enbrel treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with Enbrel, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received Enbrel. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida, Pneumocystis, Aspergillus,* and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

Autoantibodies
Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥ 1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

Pancytopenia and aplastic anaemia
There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

Interstitial lung disease
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47%

(frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Concurrent treatment with anakinra
In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

Elevated liver enzymes
In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

Autoimmune hepatitis
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

Paediatric population

See Summary of the safety profile, above.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Enbrel subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Enbrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells, including T-cells, leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of

TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etanercept, possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Clinical efficacy and safety

This section presents data from three studies in juvenile idiopathic arthritis, one study in paediatric patients with plaque psoriasis, four studies in adults with rheumatoid arthritis, and four studies in adults with plaque psoriasis.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
The safety and efficacy of Enbrel were assessed in a two-part study in 69 children with polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic onset). Patients aged 4 to 17 years with moderately to severely active polyarticular-course juvenile idiopathic arthritis refractory to, or intolerant of, methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomised to remain on Enbrel or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥ 30% worsening in three of six JRA core set criteria and ≥ 30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive Enbrel for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

Long-term safety of Enbrel monotherapy (n=103), Enbrel plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study (n=127), 60 patients with extended oligoarthritis (EO) (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with Enbrel at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Of the 127 patients in the parent study, 109 participated in the open-label extension study and were followed for an additional 8 years for a total of up to 10 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Enbrel, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Enbrel following an earlier withdrawal from treatment; and 45 (41%) had stopped Enbrel (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire follow-up period. Patients actively taking Enbrel could enter an optional withdrawal-retreatment period once during the extension study based on investigator's judgement of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥ 30% worsening in at least 3 of the 6 ACR Pedi components with ≥ 30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after Enbrel withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the small number of data points, these results should be interpreted with caution.

The safety profile was consistent with that observed in the parent study.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy. Additionally, studies have not been conducted to assess the effects of reducing the recommended dose of Enbrel following its long-term use in patients with JIA.

Paediatric patients with plaque psoriasis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by an sPGA score ≥ 3, involving ≥ 10% of the BSA, and PASI ≥ 12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received Enbrel 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to Enbrel had positive efficacy responses (e.g., PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks

	Enbrel 0.8 mg/kg Once Weekly (N = 106)	Placebo (N = 105)
PASI 75, n (%)	60 (57%)[a]	12 (11%)
PASI 50, n (%)	79 (75%)[a]	24 (23%)
sPGA "clear" or "minimal", n (%)	56 (53%)[a]	14 (13%)

Abbreviation: sPGA-static Physician Global Assessment

a. $p < 0.0001$ compared with placebo

After the 12-week double-blind treatment period, all patients received Enbrel 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to Enbrel. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of Enbrel 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with Enbrel was generally comparable to the original 48-week study and did not reveal any new safety findings.

Adult patients with rheumatoid arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively: ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; $p<0.01$ Enbrel vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

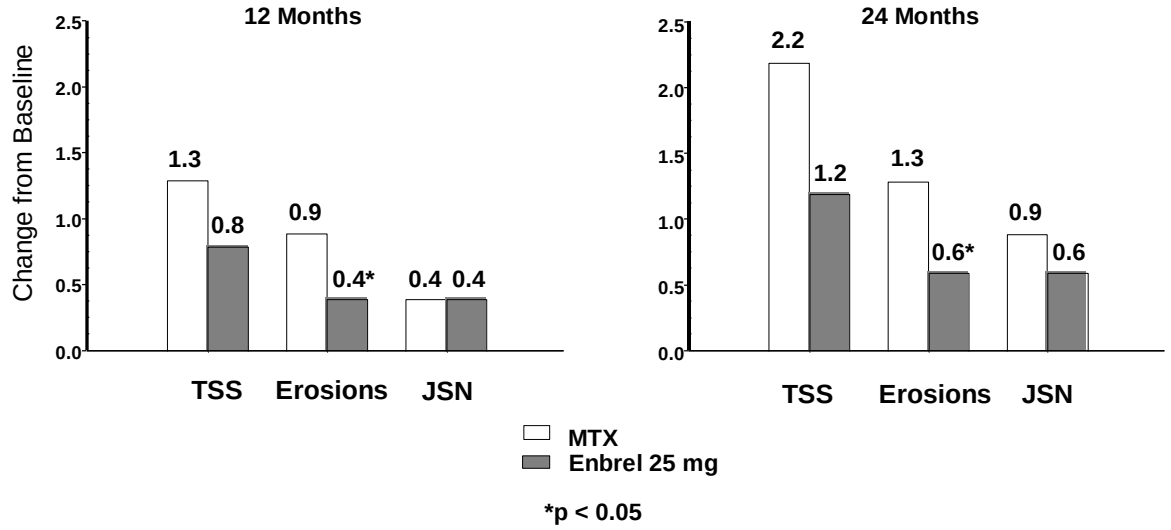
Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Enbrel was significantly better than placebo in all components of the ACR criteria, as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with Enbrel compared to controls at 3 and 6 months.

After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received Enbrel without interruption.

The efficacy of Enbrel was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (< 3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Enbrel were administered subcutaneously (SC) twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement, including onset of action within 2 weeks with Enbrel 25 mg, was similar to that seen in the previous trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

Radiographic Progression: Comparison of Enbrel vs. Methotrexate in Patients with RA of < 3 Years Duration



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months.

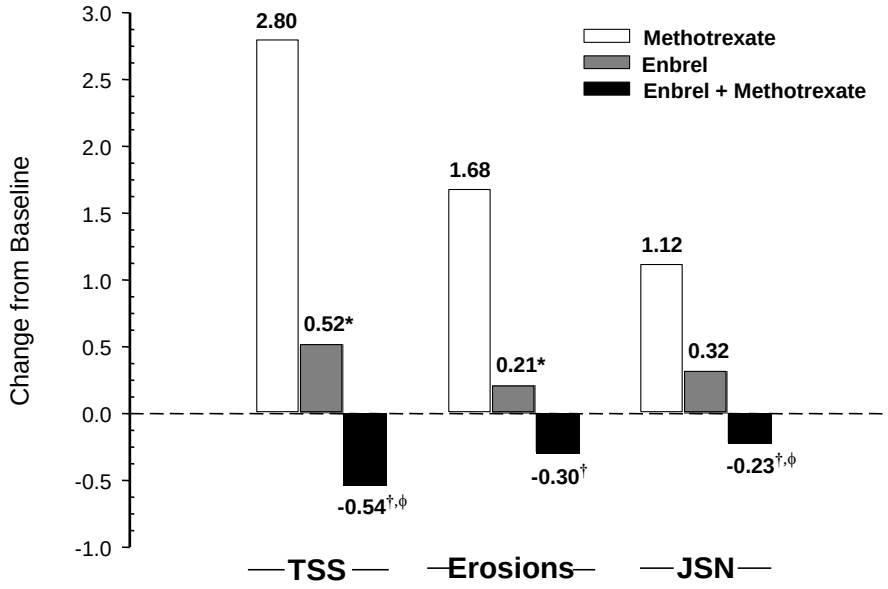
Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
ACR Responses[a]			
ACR 20	58.8%	65.5%	74.5% †,ϕ
ACR 50	36.4%	43.0%	63.2% †,ϕ
ACR 70	16.7%	22.0%	39.8% †,ϕ
DAS			
Baseline score[b]	5.5	5.7	5.5
Week 52 score[b]	3.0	3.0	2.3†,ϕ
Remission[c]	14%	18%	37%†,ϕ
HAQ			
Baseline	1.7	1.7	1.8
Week 52	1.1	1.0	0.8†,ϕ

a: Patients who did not complete 12 months in the study were considered to be non-responders.
b: Values for Disease Activity Score (DAS) are means.
c: Remission is defined as DAS <1.6.
Pairwise comparison p-values: † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. Enbrel.

Radiographic progression at 12 months was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

Radiographic Progression: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of Enbrel vs. methotrexate, † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs. Enbrel.

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p<0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p<0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens.

Adult patients with plaque psoriasis
Enbrel is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least one of the three major systemic therapies as available.

The efficacy of Enbrel versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing Enbrel with other systemic therapies. Instead, the safety and efficacy of Enbrel were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

Study 1 was a Phase 2 study in patients with active, but clinically stable, plaque psoriasis involving ≥ 10% of the body surface area who were ≥ 18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of Enbrel (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. Enbrel was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three Enbrel doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded Enbrel (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg Enbrel, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg Enbrel twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg Enbrel or placebo once weekly for 12 weeks and then all patients received open-label 50 mg Enbrel once weekly for an additional 12 weeks.

In study 1, the Enbrel-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) ($p<0.0001$). At 24 weeks, 56% of patients in the Enbrel-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

Responses of Patients with Psoriasis in Studies 2, 3 and 4

	Study 2					Study 3			Study 4	
		----------Enbrel---------				--------Enbrel-------			-------Enbrel------	
Response (%)	Placebo n = 166 wk 12	25 mg BIW n = 162 wk 12	25 mg BIW n = 162 wk 24[a]	50 mg BIW n = 164 wk 12	50 mg BIW n = 164 wk 24[a]	Placebo n = 193 wk 12	25 mg BIW n = 196 wk 12	50 mg BIW n = 196 wk 12	Placebo n = 46 wk 12	50 mg QW n = 96 wk 12	50 mg QW n = 90 wk 24[a]
PASI 50	14	58*	70	74*	77	9	64*	77*	9	69*	83
PASI 75	4	34*	44	49*	59	3	34*	49*	2	38*	71
DSGA[b], clear or almost clear	5	34*	39	49*	55	4	39*	57*	4	39*	64

*$p \leq 0.0001$ compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving Enbrel 25 mg BIW or 50 mg once weekly from week 13 to week 24.

b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received Enbrel, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned, with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with Enbrel in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Enbrel dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the Enbrel-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) ($p<0.0001$). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where Enbrel was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

Antibodies to Enbrel
Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

5.2 Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products as well as the parent compound.

Special populations

Renal impairment
Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal failure. The presence of renal impairment should not require a change in dosage.

Hepatic impairment
Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
In a polyarticular-course juvenile idiopathic arthritis trial with Enbrel, 69 patients (aged 4 to 17 years) were administered 0.4 mg Enbrel/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Paediatric patients with plaque psoriasis
Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed

in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice-weekly.

Adults

Absorption
Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 μg/ml, and the area under the curve was 235 ± 96.6 μg•hr/ml. Mean serum concentration profiles at steady state in treated RA patients were C_{max} of 2.4 mg/l vs. 2.6 mg/l, C_{min} of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg Enbrel once weekly (n=21) vs. 25 mg Enbrel twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466 μg•hr/ml and 474 μg•hr/ml for 50 mg Enbrel once weekly (N= 154) and 25 mg twice weekly (N = 148), respectively.

Distribution
A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

Elimination
Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of Enbrel in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.
There is no apparent pharmacokinetic difference between males and females.

Linearity
Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

5.3 Preclinical safety data

In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with Enbrel due to the development of neutralising antibodies in rodents.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Mannitol (E421)
Sucrose
Trometamol

Solvent

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

From a microbiological point of view, the reconstituted medicinal product should be used immediately. Chemical and physical in-use stability has been demonstrated for 6 hours at temperatures not above 25°C after reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Enbrel may be stored at temperatures up to a maximum of 25° C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks of removal from refrigeration.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear glass vial (2 ml, type I glass) with rubber stopper, aluminium seal, and flip-off plastic cap. Enbrel is supplied with pre-filled syringes containing water for injection. The syringes are type I glass. The syringe cover contains dry natural rubber (latex) (see section 4.4). Cartons contain 4 vials of Enbrel, 4 pre-filled syringes of water for injections, 4 needles, 4 vial adaptors and 8 alcohol swabs.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

Enbrel is reconstituted with 1 ml water for injections before use, and administered by subcutaneous injection. The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes or particles. Some white foam may remain in the vial – this is normal. Enbrel should not be used if all the powder in the vial is not dissolved within 10 minutes. Start again with another vial.

Comprehensive instructions for the preparation and administration of the reconstituted Enbrel vial are given in the package leaflet, section 7, "Instructions for use."

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2000
Date of last renewal: 26 November 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg solution for injection in dose-dispenser cartridge
Enbrel 50 mg solution for injection in dose-dispenser cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Enbrel 25 mg solution for injection in dose-dispenser cartridge

Each dose-dispenser cartridge contains 25 mg of etanercept.

Enbrel 50 mg solution for injection in dose-dispenser cartridge

Each dose-dispenser cartridge contains 50 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear, and colourless to pale yellow or pale brown.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Enbrel in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Enbrel can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Enbrel, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis (AS)
Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis
Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

4.2 Posology and method of administration

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients treated with Enbrel should be given the Patient Card.

The Enbrel dose-dispenser cartridge is available in 25 mg and 50 mg strengths. Other presentations of Enbrel are available in strengths of 10 mg, 25 mg, and 50 mg.

Posology

Rheumatoid arthritis
25 mg Enbrel administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis
The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque psoriasis
The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Special populations

Renal and hepatic impairment
No dose adjustment is required.

Elderly
No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

Paediatric population
The dosage of Enbrel is based on body weight for paediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using the powder and solvent for solution for injection presentations or the powder for solution for injection presentations (see below for dosing for specific indication). Patients weighing 62.5 kg or more, may be dosed using a fixed-dose pre-filled syringe, pre-filled pen, or dose-dispenser cartridge.

The safety and efficacy of Enbrel in children aged less than 2 years has not been established.
No data are available.

Juvenile idiopathic arthritis
The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.

The 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of Enbrel in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age 6 years and above)
The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of Enbrel in children aged below 6 years in the indication plaque psoriasis.

Method of administration

Subcutaneous use

The total content (0.5 ml for the 25 mg dose strength or 1 ml for the 50 mg dose strength) of the dose-dispenser cartridge should be administered using the SMARTCLIC injection device for a subcutaneous injection only. Suitable sites for injection would include the abdomen, upper thighs, or by caregiver only in the outer area of the upper arms.

Enbrel solution for injection in a dose-dispenser cartridge is intended for single-use in conjunction with the SMARTCLIC device. After proper training on the injection technique, patients may self-inject using the SMARTCLIC device with the single-use dose-dispenser cartridge if their physician determines that it is appropriate and will receive medical follow-up as necessary. The physician should discuss with the patient which injection presentation option is the most appropriate.

For administration, the instructions for use at the end of the Package Leaflet and in the user manual provided with the SMARTCLIC device should be followed (see section 6.6). Detailed instructions on unintentional dosing or scheduling variations, including missed doses, are provided in section 3 of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with Enbrel should not be initiated in patients with active infections including chronic or localised infections.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the brand name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections

Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of Enbrel (see section 4.8). These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient’s risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. The safety and efficacy of Enbrel in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or

chronic infections or with underlying conditions that may predispose patients to infections such as advanced or poorly controlled diabetes.

Tuberculosis

Cases of active tuberculosis including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported in patients treated with Enbrel.

Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the Patient Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Enbrel therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including Enbrel, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with Enbrel. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Enbrel in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, Enbrel should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving Enbrel. Enbrel should be used with caution in patients with a history of hepatitis C.

Concurrent treatment with anakinra

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus the combined use of Enbrel and anakinra is not recommended (see sections 4.5 and 4.8).

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

Allergic reactions

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated.

The needle cap of the dose-dispenser cartridge contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled by, or when Enbrel is administered to persons with known or possible latex sensitivity.

The needle cover of the pre-filled syringe in dose-dispenser cartridge contains latex (dry natural rubber). Patients or caregivers should contact their physician or healthcare professional before using Enbrel if the needle cover will be handled by or if Enbrel will be given to someone with a known or possible hypersensitivity (allergy) to latex.

Immunosuppression

The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of Enbrel in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Enbrel, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated

with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Skin cancers
Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving Enbrel compared with control patients, particularly in patients with psoriasis.

Vaccinations

Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. In a double blind, placebo controlled, randomised clinical study in adult patients with psoriatic arthritis 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower and few patients had two-fold rises in titres compared to patients not receiving Enbrel. The clinical significance of this is unknown.

Autoantibody formation

Treatment with Enbrel may result in the formation of autoimmune antibodies (see section 4.8).

Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment.

Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, Enbrel was not efficacious, and the mortality rate in patients treated with Enbrel was significantly higher after 6 months. Consequently, Enbrel should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Enbrel in patients who also have moderate to severe alcoholic hepatitis.

Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener’s granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener’s granulomatosis.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Special populations

Elderly
In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received Enbrel were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Paediatric population

Vaccinations
It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy (see Vaccinations, above).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with anakinra

Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data).

In addition, in a double-blind placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel (see sections 4.4 and 4.8). The combination Enbrel and anakinra has not demonstrated increased clinical benefit and is therefore not recommended.

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

Concurrent treatment with sulfasalazine

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

Non-interactions

In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy.

Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Enbrel should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Enbrel during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of Enbrel is generally not recommended.

Breast-feeding

In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Limited information from the published literature indicates etanercept has been detected at low levels in human milk. Etanercept could be considered for use during breast-feeding taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

While systemic exposure in a breastfed infant is expected to be low because etanercept is largely degraded in the gastrointestinal tract, limited data regarding systemic exposure in the breastfed infant are available. Therefore, the administration of live vaccines (e.g., BCG) to a breastfed infant when the mother is receiving etanercept could be considered 16 weeks after stopping breast-feeding (or at an earlier timepoint if the infant etanercept serum levels are undetectable).

Fertility

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

4.7 Effects on ability to drive and use machines

Enbrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), headache, allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for Enbrel. TNF-antagonists, such as Enbrel, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with Enbrel. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of Enbrel, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with Enbrel use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Very Rare < 1/10,000**	**Not Known (Cannot be Estimated from Available Data)**
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)*		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic infection)*	Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*		Hepatitis B reactivation, listeria
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers* (see section 4.4)	Malignant melanoma (see section 4.4), lymphoma, leukaemia		Merkel cell carcinoma (see section 4.4), Kaposi's sarcoma
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia*	Aplastic anaemia*	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders		Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*	Vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis)	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis		Worsening of symptoms of dermatomyositis

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Not Known (Cannot be Estimated from Available Data)
Nervous system disorders	Headache			CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive (see section 4.4)	New onset cardiac failure congestive (see section 4.4)		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*		
Gastrointestinal disorders			Inflammatory bowel disease			
Hepatobiliary disorders			Elevated liver enzymes*	Autoimmune hepatitis*		
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash	Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions	Toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome		
Renal and urinary disorders				Glomerulonephritis		
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*	Pyrexia				

*see Description of selected adverse reactions, below.

Description of selected adverse reactions

Malignancies and lymphoproliferative disorders
One hundred and twenty-nine new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. In a group of 2,711 plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

Injection site reactions
Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with Enbrel developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Serious infections
In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, Streptococcal fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Enbrel treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with Enbrel, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received Enbrel. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida, Pneumocystis, Aspergillus,* and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

Autoantibodies
Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥ 1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

Pancytopenia and aplastic anaemia
There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

Interstitial lung disease
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Concurrent treatment with anakinra
In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

Elevated liver enzymes
In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind

periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

Autoimmune hepatitis
In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

Undesirable effects in paediatric patients with plaque psoriasis
In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Enbrel subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Enbrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells including T-cells leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF-binding to its cell surface receptors and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors such as etanercept possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, two studies in adults with non-radiographic axial spondyloarthritis, four studies in adults with plaque psoriasis, three studies in juvenile idiopathic arthritis and one study in paediatric patients with plaque psoriasis.

Adult patients with rheumatoid arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months respectively: ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; $p < 0.01$ Enbrel vs placebo at all timepoints for both ACR 20 and ACR 50 responses).

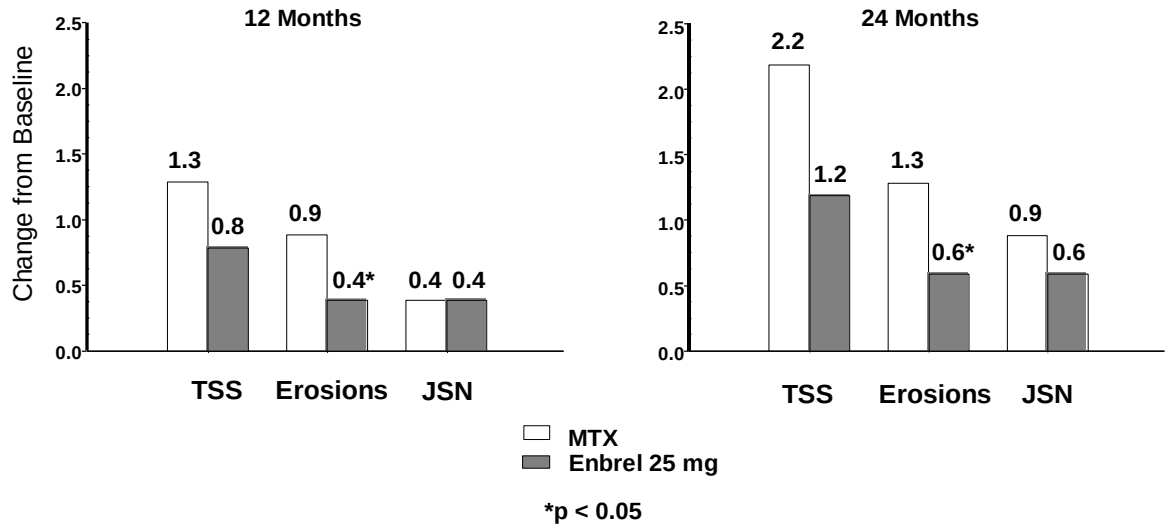
Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Enbrel was significantly better than placebo in all components of the ACR criteria as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with Enbrel compared to controls at 3 and 6 months.

After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received Enbrel without interruption.

The efficacy of Enbrel was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Enbrel were administered SC twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement including onset of action within 2 weeks with Enbrel 25 mg was similar to that seen in the previous trials, and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

Radiographic Progression: Comparison of Enbrel vs Methotrexate in Patients with RA of <3 Years Duration



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and of the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months.

Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs Methotrexate vs Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
ACR Responses[a]			
ACR 20	58.8%	65.5%	74.5% †,ϕ
ACR 50	36.4%	43.0%	63.2% †,ϕ
ACR 70	16.7%	22.0%	39.8% †,ϕ
DAS			
Baseline score[b]	5.5	5.7	5.5
Week 52 score[b]	3.0	3.0	2.3†,ϕ
Remission[c]	14%	18%	37%†,ϕ
HAQ			
Baseline	1.7	1.7	1.8
Week 52	1.1	1.0	0.8†,ϕ

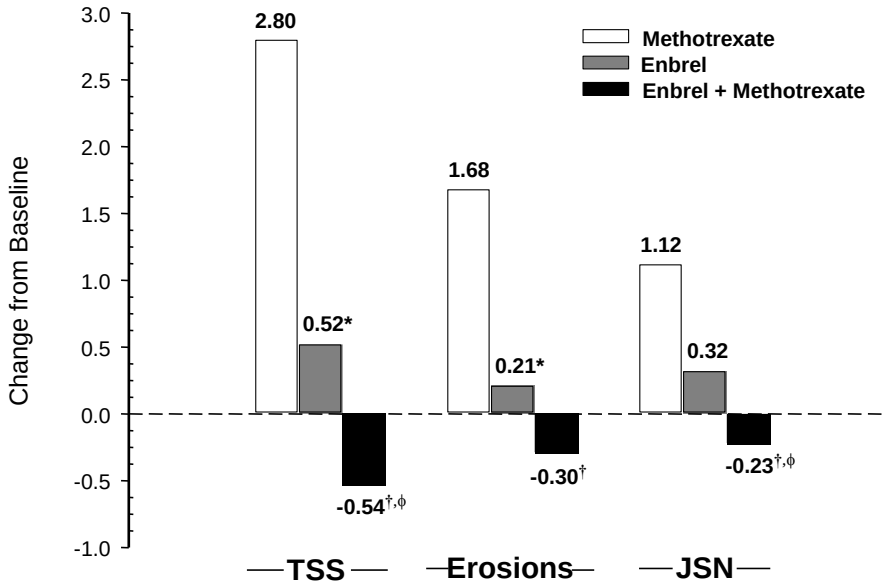
Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs Methotrexate vs Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)

a: Patients who did not complete 12 months in the study were considered to be non-responders.
b: Values for Disease Activity Score (DAS) are means.
c: Remission is defined as DAS <1.6
Pairwise comparison p-values: † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs Enbrel

Radiographic progression at 12 months was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

Radiographic Progression: Comparison of Enbrel vs Methotrexate vs Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of Enbrel vs methotrexate, † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs Enbrel

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p< 0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p< 0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens. A single 50 mg/ml injection of Enbrel was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

Adult patients with psoriatic arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients had previously been treated with NSAIDs (86%), DMARDs (80%), and corticosteroids (24%). Patients currently on methotrexate therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week methotrexate. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

Clinical responses were expressed as percentages of patients achieving the ACR 20, 50, and 70 response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table below.

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

	Percent of Patients	
	Placebo	Enbrel[a]
Psoriatic Arthritis Response	n = 104	n = 101
ACR 20		
Month 3	15	59[b]
Month 6	13	50[b]
ACR 50		
Month 3	4	38[b]
Month 6	4	37[b]
ACR 70		
Month 3	0	11[b]
Month 6	1	9[c]
PsARC		
Month 3	31	72[b]
Month 6	23	70[b]

a: 25 mg Enbrel SC twice weekly
b: $p < 0.001$, Enbrel vs. placebo
c: $p < 0.01$, Enbrel vs. placebo

Among patients with psoriatic arthritis who received Enbrel, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Enbrel was significantly better than placebo in all measures of disease activity ($p < 0.001$), and responses were similar with and without concomitant methotrexate therapy. Quality of life in psoriatic arthritis patients was assessed at every timepoint using the disability index of the HAQ. The disability index

score was significantly improved at all timepoints in psoriatic arthritis patients treated with Enbrel, relative to placebo ($p < 0.001$).

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in the Table below. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 12 months was higher in the Enbrel group compared with the placebo group (73% vs. 47%, respectively, $p \leq 0.001$). The effect of Enbrel on radiographic progression was maintained in patients who continued on treatment during the second year. The slowing of peripheral joint damage was observed in patients with polyarticular symmetrical joint involvement.

Mean (SE) Annualized Change from Baseline in Total Sharp Score

Time	Placebo (n = 104)	Etanercept (n = 101)
Month 12	1.00 (0.29)	-0.03 (0.09)[a]

SE = standard error.
a. p = 0.0001.

Enbrel treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of Enbrel in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.
No study has been performed in patients with psoriatic arthritis using the 50 mg once weekly dosing regimen. Evidence of efficacy for the once weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

Adult patients with ankylosing spondylitis
The efficacy of Enbrel in ankylosing spondylitis was assessed in 3 randomised, double-blind studies comparing twice weekly administration of 25 mg Enbrel with placebo. A total of 401 patients were enrolled from which 203 were treated with Enbrel. The largest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months in 138 patients.

The primary measure of efficacy (ASAS 20) was a ≥ 20% improvement in at least 3 of the 4 Assessment in Ankylosing Spondylitis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and absence of deterioration in the remaining domain. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% improvement, respectively.

Compared to placebo, treatment with Enbrel resulted in significant improvements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of therapy.

Responses of Patients with Ankylosing Spondylitis in a Placebo-Controlled Trial		
	Percent of Patients	
Ankylosing Spondylitis Response	Placebo N = 139	Enbrel N = 138
ASAS 20		
2 weeks	22	46[a]
3 months	27	60[a]
6 months	23	58[a]
ASAS 50		
2 weeks	7	24[a]
3 months	13	45[a]
6 months	10	42[a]
ASAS 70:		
2 weeks	2	12[b]
3 months	7	29[b]
6 months	5	28[b]
a: p <0.001, Enbrel vs. Placebo		
b: p = 0.002, Enbrel vs. placebo		

Among patients with ankylosing spondylitis who received Enbrel, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly vs 25 mg Enbrel administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once weekly and 25 mg twice weekly regimens were similar.

Adult patients with non-radiographic axial spondyloarthritis

Study 1
The efficacy of Enbrel in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received Enbrel 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. The double-blind period was followed by an open-label period during which all patients receive Enbrel 50 mg weekly for up to an additional 92 weeks. MRIs of the sacroiliac joint and spine were obtained to assess inflammation at baseline and at weeks 12 and 104.

Compared to placebo, treatment with Enbrel resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

Efficacy Response in Placebo-Controlled nr-AxSpa Study: Percent of Patients Achieving Endpoints

Double-Blind Clinical Responses at Week 12	Placebo N=106 to 109*	Enbrel N=103 to 105*
ASAS** 40	15.7	32.4[b]
ASAS 20	36.1	52.4[c]
ASAS 5/6	10.4	33.0[a]
ASAS partial remission	11.9	24.8[c]
BASDAI***50	23.9	43.8[b]

*Some patients did not provide complete data for each endpoint
**ASAS=Assessments in Spondyloarthritis International Society
***Bath Ankylosing Spondylitis Disease Activity Index
a: p <0.001, b:<0.01 and c:<0.05, respectively between Enbrel and placebo

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint (SIJ) as measured by MRI for patients receiving Enbrel. Adjusted mean change from baseline was 3.8 for Enbrel treated (n=95) versus 0.8 for placebo treated (n=105) patients (p<0.001). At week 104, the mean change from baseline in the SPARCC score measured on MRI for all Enbrel-treated subjects was 4.64 for the SIJ (n=153) and 1.40 the spine (n=154).

Enbrel showed statistically significantly greater improvement from baseline to week 12 compared to placebo in most health-related quality of life and physical function assessments, including BASFI (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D Overall Health State Score and SF-36 Physical Component Score.

Clinical responses among nr-AxSpa patients who received Enbrel were apparent at the time of the first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings. At week 104, 8 subjects had progressed to a score of bilateral Grade 2 on spinal X-ray according to the modified New York Radiological Grade, indicative of axial spondyloarthropathy.

Study 2
This multi-center, open-label, phase 4, 3-period study evaluated the withdrawal and retreatment of Enbrel in patients with active nr-AxSpa who achieved an adequate response (inactive disease defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP) less than 1.3) following 24 weeks of treatment.

209 adult patients with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the Assessment of SpondyloArthritis International Society (ASAS) classification criteria of axial spondyloarthritis (but not meeting the modified New York criteria for AS), having positive MRI findings (active inflammation on MRI highly suggestive of sacroiliitis associated with SpA) and/or positive hsCRP (defined as high sensitivity C-reactive protein [hsCRP] > 3 mg/l), and active symptoms defined by an ASDAS CRP greater than or equal to 2.1 at the screening visit received open-label Enbrel 50 mg weekly plus stable background NSAID at the optimal tolerated anti-inflammatory dosage for 24 weeks in Period 1. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. At week 24, 119 (57%) patients achieved inactive disease and entered into the Period 2 40-week withdrawal phase where subjects discontinued etanercept, yet maintained the background NSAID. The primary measure of efficacy was the occurrence of flare (defined as an ASDAS erythrocyte sedimentation rate (ESR) greater than or equal to 2.1) within 40 weeks following withdrawal of Enbrel. Patients who flared were retreated with Enbrel 50 mg weekly for 12 weeks (Period 3).

In Period 2, the proportion of patients experiencing ≥1 flare increased from 22% (25/112) at week 4 to 67% (77/115) at week 40. Overall, 75% (86/115) patients experienced a flare at any time point within 40 weeks following withdrawal of Enbrel.

The key secondary objective of Study 2 was to estimate time to flare after withdrawal of Enbrel and additionally compare the time to flare to patients from Study 1 who met the Study 2 withdrawal phase entry requirements and continued Enbrel therapy.

The median time to flare following withdrawal of Enbrel was 16 weeks (95% CI: 13-24 weeks). Less than 25% of patients in Study 1 who did not have treatment withdrawn experienced a flare over the equivalent 40-weeks as in Period 2 Study 2. The time to flare was statistically significantly shorter in subjects who discontinued Enbrel treatment (Study 2) compared to subjects who received continuous etanercept treatment (Study 1), $p<0.0001$.

Of the 87 patients who entered Period 3 and were retreated with Enbrel 50 mg weekly for 12 weeks, 62% (54/87) reachieved inactive disease, with 50% of them reachieving it within 5 weeks (95% CI: 4-8 weeks).

Adult patients with plaque psoriasis
Enbrel is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI< 50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least one of the three major systemic therapies as available.

The efficacy of Enbrel versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing Enbrel with other systemic therapies. Instead, the safety and efficacy of Enbrel were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

Study 1 was a Phase 2 study in patients with active but clinically stable plaque psoriasis involving ≥ 10% of the body surface area that were ≥ 18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of Enbrel (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. Enbrel was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three Enbrel doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded Enbrel (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg Enbrel, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg Enbrel twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg Enbrel or placebo once weekly for 12 weeks and then all patients received open-label 50 mg Enbrel once weekly for an additional 12 weeks.

In study 1, the Enbrel-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) ($p< 0.0001$). At 24 weeks, 56% of patients in the Enbrel-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

Responses of Patients with Psoriasis in Studies 2, 3 And 4

Response (%)	----------Study 2----------					----------Study 3----------			----------Study 4----------		
		----------Enbrel---------					--------Enbrel-------			-------Enbrel------	
	Placebo n = 166 wk 12	25 mg BIW n = 162 wk 12	25 mg BIW n = 162 wk 24[a]	50 mg BIW n = 164 wk 12	50 mg BIW n = 164 wk 24[a]	Placebo n = 193 wk 12	25 mg BIW n = 196 wk 12	50 mg BIW n = 196 wk 12	Placebo n = 46 wk 12	50 mg QW n = 96 wk 12	50 mg QW n = 90 wk 24[a]
PASI 50	14	58*	70	74*	77	9	64*	77*	9	69*	83
PASI 75	4	34*	44	49*	59	3	34*	49*	2	38*	71
DSGA[b], clear or almost clear	5	34*	39	49*	55	4	39*	57*	4	39*	64

*p ≤ 0.0001 compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving Enbrel 25 mg BIW or 50 mg once weekly from week 13 to week 24.

b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received Enbrel, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥ 150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with Enbrel in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Enbrel dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the Enbrel-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) ($p<0.0001$). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where Enbrel was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

Antibodies to Enbrel

Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
The safety and efficacy of Enbrel were assessed in a two-part study in 69 children with polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic onset). Patients aged 4 to 17 years with moderately to severely active polyarticular-course juvenile idiopathic arthritis refractory to, or intolerant of, methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomised to remain on Enbrel or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥ 30% worsening in three of six JRA core set criteria and ≥ 30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive Enbrel for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

Long-term safety of Enbrel monotherapy (n=103), Enbrel plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study (n=127), 60 patients with extended oligoarthritis (EO) (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with Enbrel at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi

30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Of the 127 patients in the parent study, 109 participated in the open-label extension study and were followed for an additional 8 years for a total of up to 10 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Enbrel, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Enbrel following an earlier withdrawal from treatment; and 45 (41%) had stopped Enbrel (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire follow-up period. Patients actively taking Enbrel could enter an optional withdrawal-retreatment period once during the extension study based on investigator's judgement of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥ 30% worsening in at least 3 of the 6 ACR Pedi components with ≥ 30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after Enbrel withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the small number of data points, these results should be interpreted with caution.

The safety profile was consistent with that observed in the parent study.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy. Additionally, studies have not been conducted to assess the effects of reducing the recommended dose of Enbrel following its long-term use in patients with JIA.

Paediatric patients with plaque psoriasis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by a sPGA score ≥ 3, involving ≥ 10% of the BSA, and PASI ≥ 12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received Enbrel 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to Enbrel had positive efficacy responses (e.g. PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks

	Enbrel 0.8 mg/kg Once Weekly (N = 106)	**Placebo (N = 105)**
PASI 75, n (%)	60 (57%)[a]	12 (11%)
PASI 50, n (%)	79 (75%)[a]	24 (23%)
sPGA "clear" or "minimal", n (%)	56 (53%)[a]	14 (13%)

Abbreviation: sPGA-static Physician Global Assessment.
a. $p < 0.0001$ compared with placebo.

After the 12-week double-blind treatment period, all patients received Enbrel 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to Enbrel. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of Enbrel 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with Enbrel was generally comparable to the original 48-week study and did not reveal any new safety findings.

5.2 Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products as well as the parent compound.

Absorption

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 μg/ml, and the area under the curve was 235 ± 96.6 μg•hr/ml.

Mean serum concentration profiles at steady state in treated RA patients were C_{max} of 2.4 mg/l vs. 2.6 mg/l, C_{min} of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg Enbrel once weekly (n=21) vs. 25 mg Enbrel twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466 μg•hr/ml and 474 μg•hr/ml for 50 mg Enbrel once weekly (N = 154) and 25 mg twice weekly (N = 148), respectively.

Distribution

A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of Enbrel in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.

There is no apparent pharmacokinetic difference between males and females.

Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

Special populations

Renal impairment
Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept

to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal failure. The presence of renal impairment should not require a change in dosage.

Hepatic impairment
Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

Elderly
The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

Paediatric population

Paediatric patients with juvenile idiopathic arthritis
In a polyarticular-course juvenile idiopathic arthritis trial with Enbrel, 69 patients (aged 4 to 17 years) were administered 0.4 mg Enbrel/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Paediatric patients with plaque psoriasis
Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice weekly.

5.3 Preclinical safety data

In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with Enbrel due to the development of neutralising antibodies in rodents.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium chloride
L-Arginine hydrochloride
Sodium phosphate monobasic dihydrate
Sodium phosphate dibasic dihydrate

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Enbrel may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks of removal from refrigeration.

Keep the dose-dispenser cartridges in the outer carton in order to protect from light.

6.5 Nature and contents of container

25 mg solution for injection in dose-dispenser cartridge
Dose-dispenser cartridge with integrated 25 mg pre-filled Enbrel syringe. The pre-filled syringe inside the dose-dispenser cartridge is made from clear type 1 glass with a staked stainless steel 27 gauge needle, rigid needle cover, and rubber stopper. The rigid needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Cartons contain 4, 8 or 24 Enbrel dose-dispenser cartridges with 8, 16 or 48 alcohol swabs. Not all pack sizes may be marketed.

50 mg solution for injection in dose-dispenser cartridge
Dose-dispenser cartridge with integrated 50 mg pre-filled Enbrel syringe. The pre-filled syringe inside the dose-dispenser cartridge is made from clear type 1 glass with a staked stainless steel 27 gauge needle, rigid needle cover, and rubber stopper. The rigid needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Cartons contain 2, 4 or 12 Enbrel dose-dispenser cartridges with 4, 8 or 24 alcohol swabs. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

Before injection, Enbrel dose-dispenser cartridges should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the dose-dispenser cartridge to reach room temperature. By looking through the inspection window, the solution should be clear to slightly opalescent, colourless to pale yellow or pale brown and may contain small white or almost transparent particles of protein.

Comprehensive instructions for the preparation and administration of Enbrel dose-dispenser cartridge are given in the package leaflet and in the user manual provided with the SMARTCLIC device.

This medicinal product (dose-dispenser cartridge) is for single use only in conjunction with the SMARTCLIC device.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Enbrel 25 mg solution for injection in dose-dispenser cartridge
EU/1/99/126/027
EU/1/99/126/028
EU/1/99/126/029

Enbrel 50 mg solution for injection in dose-dispenser cartridge
EU/1/99/126/030
EU/1/99/126/031
EU/1/99/126/032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2000
Date of last renewal: 26 November 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Pfizer Ireland Pharmaceuticals Unlimited Company
Grange Castle Business Park
Nangor Road
Dublin 22
D22 V8F8
Ireland

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Belgium NV
Rijksweg 12,
2870 Puurs-Sint-Amands
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the use of etanercept in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media,

distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at reducing the risk of serious infections and ensuring the traceability of etanercept drug product.

The MAH shall ensure that in each Member State where etanercept is marketed, all healthcare professionals who are expected to prescribe etanercept and all patients who are expected to use etanercept have access to/are provided with the following educational materials:

- Patient Card
    - Patient Cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides the following important safety information for patients:
        - Etanercept treatment may increase the risk of infection
        - Signs or symptoms of this safety concern and when to seek attention from a healthcare professional
        - Instructions to record the brand name and batch number of the medication to ensure traceability
        - Contact details of the etanercept prescriber

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT – EU/1/99/126/002

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg powder for solution for injection
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of Enbrel contains 25 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Powder: Mannitol, sucrose and trometamol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
4 vials of powder
8 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

After preparing the Enbrel solution, immediate use is recommended (up to a maximum of 6 hours).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

You will also need 1 ml of water for injections and a syringe to administer Enbrel

16. INFORMATION IN BRAILLE

Enbrel 25 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR VIAL LABEL – EU/1/99/126/002

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enbrel 25 mg powder for injection
etanercept
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT FOR TRAY BACKING – EU/1/99/126/002

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg powder for solution for injection
etanercept

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT – EU/1/99/126/003-005

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg powder and solvent for solution for injection
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of Enbrel contains 25 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Powder: Mannitol, sucrose and trometamol
Solvent: Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

4 vials of powder
4 pre-filled syringes of 1 ml solvent
4 stainless steel injection needles
4 vial adaptors
8 alcohol swabs

8 vials of powder
8 pre-filled syringes of 1 ml solvent
8 stainless steel injection needles
8 vial adaptors
16 alcohol swabs

24 vials of powder
24 pre-filled syringes of 1 ml solvent
24 stainless steel injection needles
24 vial adaptors
48 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

After preparing the Enbrel solution, immediate use is recommended (up to a maximum of 6 hours).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/003 4 vials
EU/1/99/126/004 8 vials
EU/1/99/126/005 24 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enbrel 25 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR VIAL LABEL – EU/1/99/126/003-005

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enbrel 25 mg powder for injection
etanercept
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR SYRINGE LABEL – EU/1/99/126/003-005

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Enbrel
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT FOR TRAY BACKING – EU/1/99/126/003-005

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg powder and solvent for solution for injection
etanercept

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT – EU/1/99/126/013-015, EU/1/99/126/026 (25 mg Pre-filled Syringe)

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg solution for injection in pre-filled syringe
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe of Enbrel contains 25 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

4 pre-filled syringes
4 alcohol swabs

8 pre-filled syringes
8 alcohol swabs

12 pre-filled syringes
12 alcohol swabs

24 pre-filled syringes
24 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

Injection advice:
Inject the solution after it has reached room temperature (15 to 30 minutes after taking the product from the refrigerator).
Inject slowly, at an angle of 45° to 90° to the skin.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/013 4 pre-filled syringes
EU/1/99/126/014 8 pre-filled syringes
EU/1/99/126/015 24 pre-filled syringes
EU/1/99/126/026 12 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enbrel 25 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR PRE-FILLED SYRINGE LABEL – EU/1/99/126/013-015, EU/1/99/126/026 (25 mg Pre-filled Syringe)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enbrel 25 mg injection
etanercept
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 mg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT – EU/1/99/126/016-018 (50 mg Pre-filled Syringe)

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 50 mg solution for injection in pre-filled syringe
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe of Enbrel contains 50 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection in pre-filled syringe

2 pre-filled syringes
2 alcohol swabs

4 pre-filled syringes
4 alcohol swabs

12 pre-filled syringes
12 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

Injection advice:
Inject the solution after it has reached room temperature (15 to 30 minutes after taking the product from the refrigerator).
Inject slowly, at an angle of 45° to 90° to the skin.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/016 2 pre-filled syringes
EU/1/99/126/017 4 pre-filled syringes
EU/1/99/126/018 12 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enbrel 50 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR PRE-FILLED SYRINGE – EU/1/99/126/016-018 (50 mg Pre-filled Syringe)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enbrel 50 mg injection
etanercept
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg/1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT – EU/1/99/126/019-021 (50 mg Pre-filled Pen)

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 50 mg solution for injection in pre-filled pen
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of Enbrel contains 50 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen (MYCLIC)

2 MYCLIC pre-filled pens
2 alcohol swabs

4 MYCLIC pre-filled pens
4 alcohol swabs

12 MYCLIC pre-filled pens
12 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

Injection advice:
Inject the solution after it has reached room temperature (15 to 30 minutes after taking the product from the refrigerator).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

Keep the pre-filled pens in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/019 2 pre-filled pens
EU/1/99/126/020 4 pre-filled pens
EU/1/99/126/021 12 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enbrel 50 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR PRE-FILLED PEN – EU/1/99/126/019-021 (50 mg Pre-filled Pen)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enbrel 50 mg solution for injection in pre-filled pen
etanercept
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg/1 ml

6. OTHER

MYCLIC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT – EU/1/99/126/022 (For paediatric use)

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 10 mg powder and solvent for solution for injection for paediatric use
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of Enbrel contains 10 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Powder: Mannitol, sucrose and trometamol
Solvent: Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

4 vials of powder
4 pre-filled syringes of 1 ml solvent
4 stainless steel injection needles
4 vial adaptors
8 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

The 10 mg vial is for children prescribed a dose of 10 mg or less. Follow the directions given by the doctor.

Each vial should be used for just one dose in one patient, and any remaining solution should be discarded.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

After preparing the Enbrel solution, immediate use is recommended (up to a maximum of 6 hours).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/022

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enbrel 10 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR VIAL LABEL – EU/1/99/126/022 (For paediatric use)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enbrel 10 mg powder for injection
etanercept
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR SYRINGE LABEL – EU/1/99/126/022 (For paediatric use)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Enbrel
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT FOR TRAY BACKING – EU/1/99/126/022 (For paediatric use)

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 10 mg
etanercept

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT – EU/1/99/126/023-025 (25 mg Pre-filled Pen)

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg solution for injection in pre-filled pen
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of Enbrel contains 25 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen (MYCLIC)

4 MYCLIC pre-filled pens
4 alcohol swabs

8 MYCLIC pre-filled pens
8 alcohol swabs

24 MYCLIC pre-filled pens
24 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

Injection advice:
Inject the solution after it has reached room temperature (15 to 30 minutes after taking the product from the refrigerator).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

Keep the pre-filled pens in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/023 4 pre-filled pens
EU/1/99/126/024 8 pre-filled pens
EU/1/99/126/025 24 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enbrel 25 mg

17. UNIQUE IDENTIFIER-2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER-HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

TEXT FOR PRE-FILLED PEN – EU/1/99/126/023-025 (25 mg Pre-filled Pen)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enbrel 25 mg solution for injection in pre-filled pen
etanercept
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 mg/0.5 ml

6. OTHER

MYCLIC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – EU/1/99/126/027-029 (25 mg Dose-Dispenser Cartridge)

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg solution for injection in dose-dispenser cartridge
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose-dispenser cartridge of Enbrel contains 25 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in dose-dispenser cartridge

4 single-use dose-dispenser cartridges for use in SMARTCLIC device only
8 alcohol swabs

8 single-use dose-dispenser cartridges for use in SMARTCLIC device only
16 alcohol swabs

24 single-use dose-dispenser cartridges for use in SMARTCLIC device only
48 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

Injection advice:
Inject the solution after it has reached room temperature (15 to 30 minutes after taking the product from the refrigerator).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

Keep the dose-dispenser cartridges in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/027 4 dose-dispenser cartridges
EU/1/99/126/028 8 dose-dispenser cartridges
EU/1/99/126/029 24 dose-dispenser cartridges

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enbrel 25 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – EU/1/99/126/030-032 (50 mg Dose-dispenser cartridge)

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 50 mg solution for injection in dose-dispenser cartridge
etanercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose-dispenser cartridge of Enbrel contains 50 mg etanercept.

3. LIST OF EXCIPIENTS

The other ingredients in Enbrel are:
Sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in dose-dispenser cartridge

2 single-use dose-dispenser cartridges for use in SMARTCLIC device only
4 alcohol swabs

4 single-use dose-dispenser cartridges for use in SMARTCLIC device only
8 alcohol swabs

12 single-use dose-dispenser cartridges for use in SMARTCLIC device only
24 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

Injection advice:
Inject the solution after it has reached room temperature (15 to 30 minutes after taking the product from the refrigerator).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Refer to package leaflet for alternative storage details.

Keep the dose-dispenser cartridges in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/030 2 dose-dispenser cartridges
EU/1/99/126/031 4 dose-dispenser cartridges
EU/1/99/126/032 12 dose-dispenser cartridges

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enbrel 50 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DOSE-DISPENSER CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Enbrel 25 mg injection
Enbrel 50 mg injection
etanercept
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml
1 ml

6. OTHER

Needle end

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Enbrel 25 mg powder for solution for injection
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

Information in this leaflet is organised under the following 7 sections:

1. What Enbrel is and what it is used for
2. What you need to know before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Contents of the pack and other information
7. Instructions for use

1. What Enbrel is and what it is used for

Enbrel is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Enbrel works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Enbrel can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis,** and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For rheumatoid arthritis, Enbrel is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Enbrel can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, Enbrel can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), Enbrel can slow down the structural damage to those joints caused by the disease.

Enbrel is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:

- Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years

- Psoriatic arthritis in patients from the age of 12 years

- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them

- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Enbrel

Do not use Enbrel

- if you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if you or the child have, or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child, have an infection of any kind. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Enbrel.

- **Allergic reactions:** If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Infections/surgery:** If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Enbrel. Treatment with Enbrel may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Enbrel.
- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.

- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Enbrel.
  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
  Children and adults taking Enbrel may have an increased risk of developing lymphoma or another cancer.
  Some children and teenage patients who have received Enbrel or other medicines that work the same way as Enbrel have developed cancers, including unusual types, which sometimes resulted in death.
  Some patients receiving Enbrel have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Enbrel. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Alcohol abuse:** Enbrel should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- **Wegener's granulomatosis:** Enbrel is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines:** Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Enbrel.

Children and adolescents

Vaccinations: If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult your doctor before you or the child receive any vaccines.

Enbrel should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

Other medicines and Enbrel

Tell your doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use Enbrel with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Enbrel should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Enbrel during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Enbrel in pregnancy, compared with mothers who had not received Enbrel or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Enbrel in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Enbrel during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines

The use of Enbrel is not expected to affect the ability to drive or use machines.

3. How to use Enbrel

Always use this medicine exactly as the doctor has told you. Check with the doctor or pharmacist if you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or pharmacist.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Enbrel.

Plaque psoriasis

The usual dose is 25 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doctor will decide how long you should take Enbrel and whether retreatment is needed based on your response. If Enbrel has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Enbrel per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Enbrel per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of Enbrel per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Enbrel has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

Enbrel can be taken with or without food or drink.

The powder must be dissolved before use. **Detailed instructions on how to prepare and inject Enbrel are provided in section 7, "Instructions for use."** Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Enbrel

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg

- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- **Signs of cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.
The known side effects of Enbrel include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in10 people):
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people):
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people):
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is

uncommon); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi's sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Additional side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enbrel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Before preparing the Enbrel solution, Enbrel may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that Enbrel is removed from the refrigerator and the date after which Enbrel should be discarded (no more than 4 weeks following the removal from the refrigerator).

After preparing the Enbrel solution, immediate use is recommended. However, the solution may be used for up to 6 hours when stored at temperatures of up to 25°C.

Do not use this medicine if you notice the solution is not clear or contains particles. The solution should be clear, colourless to pale yellow or pale brown, with no lumps or flakes or particles.

Carefully dispose of any Enbrel solution that has not been injected within 6 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enbrel contains

The active substance in Enbrel is etanercept. Each vial of Enbrel 25 mg contains 25 mg of etanercept.

The other ingredients are:
Powder: Mannitol (E421), sucrose and trometamol

What Enbrel looks like and contents of the pack

Enbrel 25 mg is supplied as a white powder for solution for injection (powder for injection). Each pack contains 4 single-dose vials and 8 alcohol swabs.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

7. Instructions for use

This section is divided into the following sub-sections:

a. Introduction
b. Setting up for an injection
c. Preparing the Enbrel dose for injection
d. Adding water for injections

e. Withdrawing the Enbrel solution from the vial
f. Choosing an injection site
g. Preparing the injection site and injecting the Enbrel solution
h. Disposing of supplies

a. Introduction

The following instructions explain how to prepare and inject Enbrel. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the techniques of self-injection or on giving an injection to a child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

This injection should not be mixed with any other medicine.

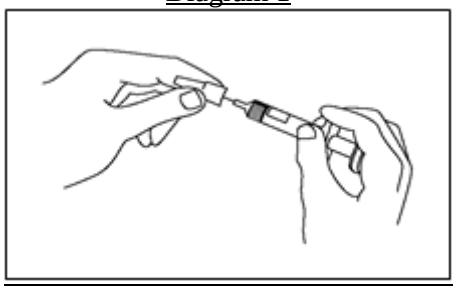
b. Setting up for an injection

- Wash your hands thoroughly.
- Select a clean, well-lit, flat working surface.
- Take the ENBREL vial out of the refrigerator and place it on a flat surface.
- You will also need the following items:
  A sterile syringe and needle(s) of 25 gauge x 16 mm or similar
  A vial or ampoule of water for injections
  2 alcohol swabs
- Inspect the expiry dates on both the Enbrel vial label and the water for injections. They should not be used after the month and year shown.

c. Preparing the Enbrel dose for injection

- Remove the plastic cap from the Enbrel vial. **Do NOT** remove the grey stopper or aluminium ring around the top of the vial.
- Use a new alcohol swab to clean the grey stopper on the Enbrel vial. After cleaning, do not touch the stopper with your hands.
- Check that a needle is on your syringe; if you are not sure how to attach a needle ask your doctor or nurse.
- Remove the needle cover by firmly pulling it straight off the syringe taking care not to touch the needle or allow the needle to touch any surfaces (see Diagram 1). Be careful not to bend or twist the cover during removal to avoid damage to the needle.

Diagram 1



- Check your syringe contains 1 ml of water for injections.
- If you are not sure how to fill your syringe ask your doctor or nurse.
- Make sure your syringe does not contain any air bubbles.
- With the Enbrel vial upright on a flat surface, such as a table, insert the syringe needle straight down through the centre ring of the grey stopper of the vial (see Diagram 2). If the needle is correctly lined up, you should feel a slight resistance and then a "*pop"* as the needle goes through the centre of the stopper. Look for the needle tip inside the stopper window (see

Diagram 3). If the needle is not correctly lined up, you will feel constant resistance as it goes through the stopper and no "*pop"*. Do not insert the needle at an angle, this may cause the needle to bend and/or prevent proper addition of the solvent into the vial (see Diagram 4).

Diagram 2

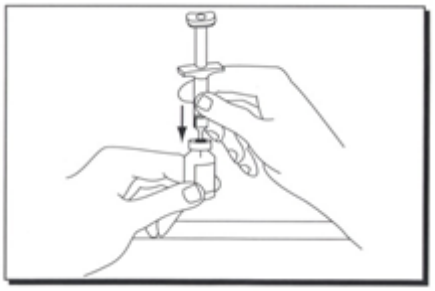


Diagram 3

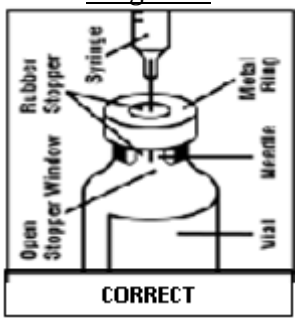
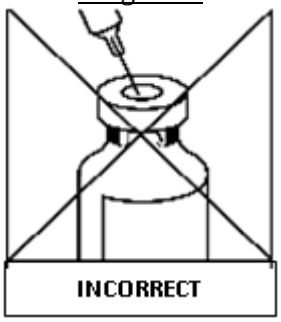


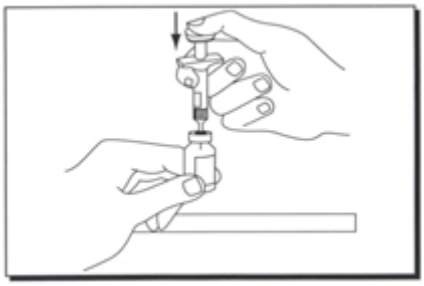
Diagram 4



d. Adding water for injections

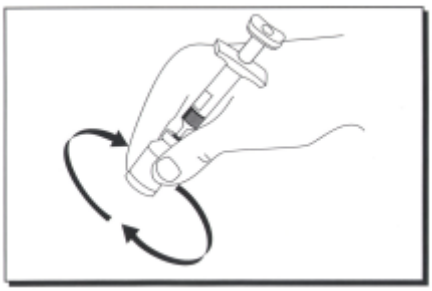
- Push the plunger in **VERY SLOWLY** until all the water for injections is in the vial. This will help reduce foaming (lots of bubbles) (see Diagram 5).

Diagram 5



- Leave the syringe in place. Gently move the vial in circles a few times, to dissolve the powder (see Diagram 6). **Do NOT** shake the vial. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes, or particles. Some white foam may remain in the vial this is normal. **Do NOT** use Enbrel if all the powder in the vial is not dissolved within 10 minutes. Start again with a new Enbrel vial, water for injections, syringe, needle and swabs.

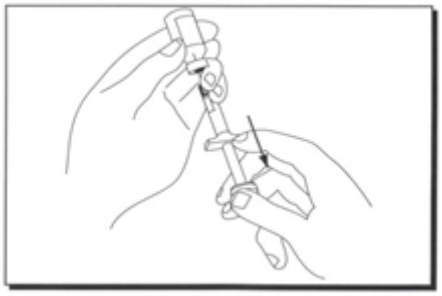
Diagram 6



e. Withdrawing the Enbrel solution from the vial

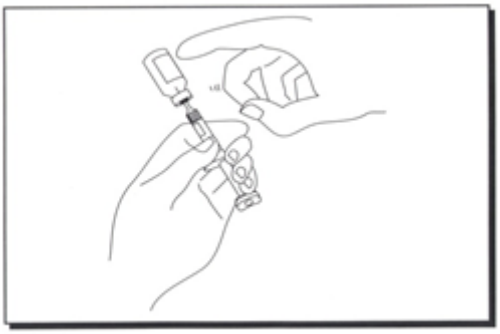
- With the needle still in the vial, hold the vial upside down at eye level. Slowly pull the plunger back to draw the liquid into the syringe (see Diagram 7). As the liquid level drops in the vial, you may need to withdraw the needle partially to keep the tip of the needle in the liquid. For adult patients, withdraw the entire volume. For children, remove only the portion of liquid as directed by your child's doctor.

Diagram 7



- With the needle still inserted in the vial, check the syringe for air bubbles. Gently tap the syringe to make any bubbles rise to the top of the syringe, near the needle (see Diagram 8). Slowly press the plunger to push bubbles out of the syringe and into the vial. When you do this, if you accidentally push liquid back into the vial, slowly pull the plunger to draw the liquid back into the syringe.

Diagram 8



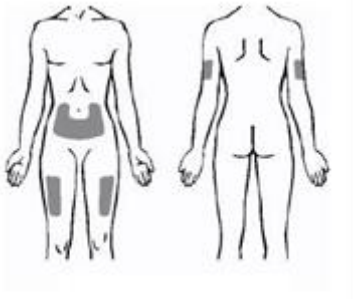
- Pull the needle completely out of the vial. Again, do not touch the needle or allow it to touch any surface.

(Note: After you have completed these steps, a small amount of liquid may remain in the vial. This is normal.)

f. Choosing an injection site

- The three recommended injection sites for Enbrel include: (1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right around the navel; and (3) the outer area of the upper arms (see Diagram 9). If you are self injecting, you should not use the outer area of the upper arms.

Diagram 9

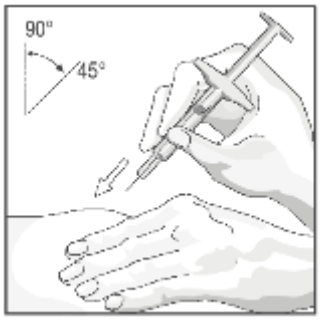


- A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
- If you or the child have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skin lesions").

g. Preparing the injection site and injecting the Enbrel solution

- Wipe the site where Enbrel is to be injected with an alcohol swab, using a circular motion. **Do NOT** touch this area again before giving the injection.
- When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
- With a quick, short motion, push the needle all the way into the skin at an angle between 45° and 90° (see Diagram 10). With experience, you will find the angle that is most comfortable for you or the child. Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 10



- When the needle is completely inserted into the skin, release the skin that you are holding. With your free hand, hold the syringe near its base to stabilise it. Then push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 11).

Diagram 11



- When the syringe is empty, remove the needle from the skin, being careful to keep it at the same angle it was when it was inserted.
- Press a cotton ball over the injection site for 10 seconds. Slight bleeding may occur. **Do NOT** rub the injection site. A bandage is optional.

h. Disposing of supplies

- The syringe and needle should **NEVER** be re-used. **Never** recap a needle. Dispose of the needle and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with Enbrel.

Package leaflet: Information for the user

Enbrel 25 mg powder and solvent for solution for injection
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

Information in this leaflet is organised under the following 7 sections:

1. What Enbrel is and what it is used for
2. What you need to know before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Contents of the pack and other information
7. Instructions for use

1. What Enbrel is and what it is used for

Enbrel is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Enbrel works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Enbrel can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis,** and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For rheumatoid arthritis, Enbrel is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Enbrel can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, Enbrel can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), Enbrel can slow down the structural damage to those joints caused by the disease.

Enbrel is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:

- Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
- Psoriatic arthritis in patients from the age of 12 years

- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them
- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Enbrel

Do not use Enbrel

- if you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if you or the child have, or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child have an infection of any kind. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Enbrel.

- **Allergic reactions:** If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Latex:** The syringe rubber tip is made from latex (dry natural rubber). Contact your doctor before using Enbrel if the syringe will be handled by, or Enbrel will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Infections/surgery:** If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Enbrel. Treatment with Enbrel may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Enbrel.
- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.

- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.
- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Enbrel.
  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
  Children and adults taking Enbrel may have an increased risk of developing lymphoma or another cancer.
  Some children and teenage patients who have received Enbrel or other medicines that work the same way as Enbrel have developed cancers, including unusual types, which sometimes resulted in death.
  Some patients receiving Enbrel have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Enbrel. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Alcohol abuse:** Enbrel should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- **Wegener's granulomatosis:** Enbrel is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines:** Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Enbrel.

Children and adolescents

Vaccinations: If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult your doctor before you or the child receive any vaccines.

Enbrel should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

Other medicines and Enbrel

Tell your doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use Enbrel with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Enbrel should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Enbrel during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Enbrel in pregnancy,

compared with mothers who had not received Enbrel or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Enbrel in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Enbrel during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines

The use of Enbrel is not expected to affect the ability to drive or use machines.

3. How to use Enbrel

Always use this medicine exactly as the doctor has told you. Check with the doctor or pharmacist if you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or pharmacist.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Enbrel.

Plaque psoriasis

The usual dose is 25 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doctor will decide how long you should take Enbrel and whether retreatment is needed based on your response. If Enbrel has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Enbrel per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Enbrel per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of Enbrel per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Enbrel has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

Enbrel can be taken with or without food or drink.

The powder must be dissolved before use. **Detailed instructions on how to prepare and inject Enbrel are provided in section 7, "Instructions for use."** Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Enbrel

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- **Signs of cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

The known side effects of Enbrel include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people):
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people):
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people):
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to

those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi's sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Additional side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enbrel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Before preparing the Enbrel solution, Enbrel may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that Enbrel is removed from the refrigerator and the date after which Enbrel should be discarded (no more than 4 weeks following the removal from the refrigerator).

After preparing the Enbrel solution, immediate use is recommended. However, the solution may be used for up to 6 hours when stored at temperatures of up to 25°C.

Do not use this medicine if you notice the solution is not clear or contains particles. The solution should be clear, colourless to pale yellow or pale brown, with no lumps or flakes or particles.

Carefully dispose of any Enbrel solution that has not been injected within 6 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enbrel contains

The active substance in Enbrel is etanercept. Each vial of Enbrel 25 mg contains 25 mg of etanercept.
The other ingredients are:
Powder: Mannitol (E421), sucrose and trometamol
Solvent: Water for injections

What Enbrel looks like and contents of the pack

Enbrel 25 mg is supplied as a white powder and solvent for solution for injection (powder for injection). Each pack contains 4, 8 or 24 single dose vials, 4, 8 or 24 pre-filled syringes of water for injections, 4, 8 or 24 needles, 4, 8 or 24 vial adaptors and 8, 16 or 48 alcohol swabs. Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

7. Instructions for use

This section is divided into the following sub-sections:

a. Introduction
b. Setting up for an injection
c. Preparing the Enbrel dose for injection
d. Adding solvent
e. Withdrawing the Enbrel solution from the vial
f. Placing the needle on the syringe
g. Choosing an injection site
h. Preparing the injection site and injecting the Enbrel solution
i. Disposing of supplies

a. Introduction

The following instructions explain how to prepare and inject Enbrel. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the techniques of self-injection or on giving an injection to a child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

This injection should not be mixed with any other medicine.

b. Setting up for an injection

- Wash your hands thoroughly.
- Select a clean well-lit, flat working surface.
- The dose tray should contain the items listed below. (If not, don't use the dose tray and consult your pharmacist). Use only the items listed. **Do NOT** use any other syringe.
  1 Enbrel vial
  1 Pre-filled syringe containing clear, colourless solvent (water for injections)
  1 Needle
  1 Vial adaptor
  2 Alcohol swabs
- Inspect the expiry dates on both the vial label and the syringe label. They should not be used after the month and year shown.

c. Preparing the Enbrel dose for injection

- Remove the contents of the tray
- Remove the plastic cap from the Enbrel vial (see Diagram 1). **Do NOT** remove the grey stopper or aluminium ring around the top of the vial.

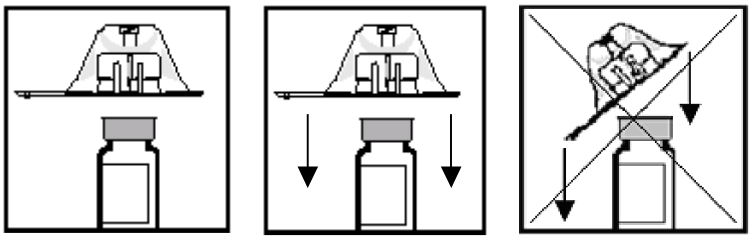
Diagram 1



- Use a new alcohol swab to clean the grey stopper on the Enbrel vial. After cleaning, do not touch the stopper with your hands or allow it to touch any surface.

- Place the vial upright on a clean, flat surface.
- Remove the paper backing from the vial adaptor package.
- While still in the plastic package, place the vial adaptor on top of the Enbrel vial so that the vial adaptor spike is centered within the raised circle on top of the vial stopper (see Diagram 2).
- Hold the vial firmly on the flat surface with one hand. With the other hand, push **STRAIGHT DOWN FIRMLY** on the adaptor package until you feel the adaptor spike penetrate the vial stopper and **FEEL AND HEAR THE ADAPTOR RIM LOCK INTO PLACE** (see Diagram 3). **Do NOT** push down the adaptor at an angle (see Diagram 4). It is important that the vial adaptor spike completely penetrates the vial stopper.

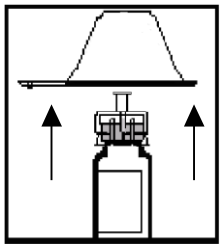
Diagram 2. Diagram 3. Diagram 4.



CORRECT **INCORRECT**

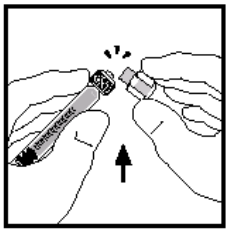
- While holding the vial in one hand, remove the plastic packaging from the vial adaptor (see Diagram 5).

Diagram 5.



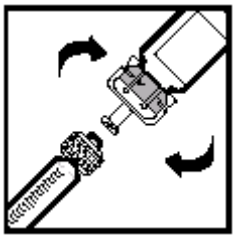
- Remove the protective cover from the syringe tip by breaking the white cap along the perforation. This is done by holding the collar of the white cap while grasping the end of the white cap with the other hand and bending it down and then up until it is broken (see Diagram 6). **Do NOT remove the white collar that remains on the syringe**.

Diagram 6



- Do not use the syringe if this perforation is already broken. Start again with another dose tray.
- Holding the glass barrel of the syringe (not the white collar) in one hand, and the vial adaptor (not the vial) in the other, connect the syringe to the vial adaptor by inserting the tip into the opening and turn clockwise until completely secured (see Diagram 7).

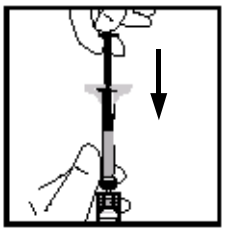
Diagram 7



d. Adding solvent

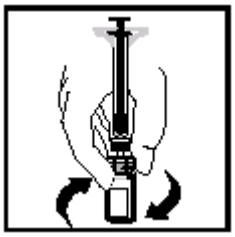
- While holding the vial upright on the flat surface, push the plunger VERY SLOWLY until all the solvent is in the vial. This will help to reduce foaming (lots of bubbles) (see Diagram 8).
- Once the solvent is added to the Enbrel, the plunger may move up by itself. This is due to air pressure and should not be of concern.

Diagram 8



- With the syringe still attached, gently move the vial in circles a few times, to dissolve the powder (see Diagram 9). **Do NOT** shake the vial. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes, or particles. Some white foam may remain in the vial this is normal. **Do NOT** use Enbrel if all the powder in the vial is not dissolved within 10 minutes. Start again with another dose tray.

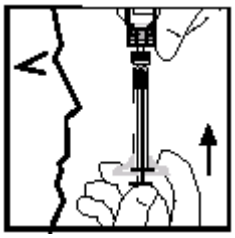
Diagram 9



e. Withdrawing the Enbrel solution from the vial

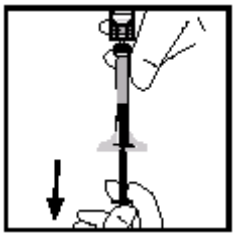
- With the syringe still attached to the vial and vial adaptor, hold the vial upside down at eye level. Push the plunger all the way into the syringe (see Diagram 10).

Diagram 10



- Then, slowly pull the plunger back to draw the liquid into the syringe (see Diagram 11). For adult patients, withdraw the entire volume. For children, remove only the portion of liquid as directed by your child's doctor. After you have withdrawn the Enbrel from the vial, you may have some air in the syringe. Do not be concerned, as you will remove the air in a later step.

Diagram 11



- With the vial held upside down, unscrew the syringe from the vial adaptor by turning it anti-clockwise (see Diagram 12).

Diagram 12



- Place the filled syringe on the clean, flat surface. Make sure that the tip does not touch anything. Be careful not to push down on the plunger.

(Note: After you have completed these steps, a small amount of liquid may remain in the vial. This is normal.)

f. Placing the needle on the syringe

- The needle has been placed in a plastic container to keep it sterile.
- To open the plastic container, hold the short, wide end in one hand. Place your other hand on the longer portion of the container.
- To break the seal, bend the larger end down and then up until broken (see Diagram 13).

Diagram 13



- Once the seal has been broken, remove the short, wide end of the plastic container.
- The needle will remain in the long part of the package.
- While holding the needle and container in one hand, pick up the syringe and insert the syringe tip into the needle opening.
- Attach the syringe to the needle by turning it clockwise until completely secured (see Diagram 14).

Diagram 14



- Remove the needle cover by firmly pulling it straight off the syringe taking care not to touch the needle or allow the needle to touch any surfaces (see Diagram 15). Be careful not to bend or twist the cover during removal to avoid damage to the needle.

Diagram 15



- While holding the syringe upright, remove any air bubbles by slowly pushing on the plunger until the air is removed (see Diagram 16).

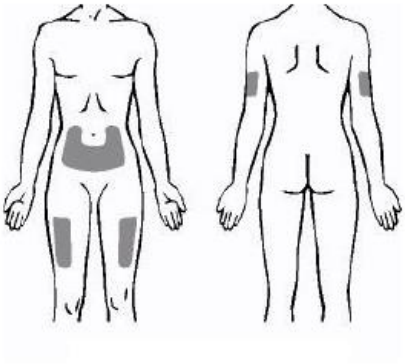
Diagram 16



g. Choosing an injection site

- The three recommended injection sites for Enbrel include: (1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right around the navel; and (3) the outer area of the upper arms (see Diagram 17). If you are self injecting, you should not use the outer area of the upper arms.

Diagram 17

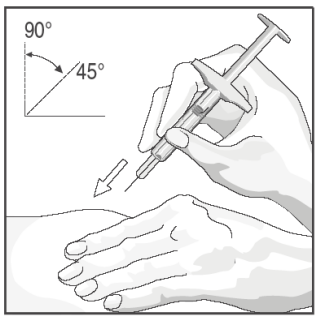


- A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. **Do NOT** inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
- If you or the child have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skin lesions").

h. Preparing the injection site and injecting the Enbrel solution

- Wipe the site where Enbrel is to be injected with an alcohol swab, using a circular motion. **Do NOT** touch this area again before giving the injection.
- When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
- With a quick, short motion, push the needle all the way into the skin at an angle between 45° and 90° (see Diagram 18). With experience, you will find the angle that is most comfortable for you or the child. Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 18



- When the needle is completely inserted into the skin, release the skin that you are holding. With your free hand, hold the syringe near its base to stabilise it. Then push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 19).

Diagram 19



- When the syringe is empty, remove the needle from the skin; being careful to keep it at the same angle it was when it was inserted.
- Press a cotton ball over the injection site for 10 seconds. Slight bleeding may occur. **Do NOT** rub the injection site. A bandage is optional.

i. Disposing of supplies

- The syringe and needles should **NEVER** be re-used. Dispose of the needles and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with Enbrel.

Package leaflet: Information for the user

Enbrel 25 mg solution for injection in pre-filled syringe
Enbrel 50 mg solution for injection in pre-filled syringe
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

Information in this leaflet is organised under the following 7 sections:

1. What Enbrel is and what it is used for
2. What you need to know before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Contents of the pack and other information
7. Instructions for use

1. What Enbrel is and what it is used for

Enbrel is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Enbrel works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Enbrel can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis,** and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For rheumatoid arthritis, Enbrel is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Enbrel can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, Enbrel can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), Enbrel can slow down the structural damage to those joints caused by the disease.

Enbrel is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
    - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
    - Psoriatic arthritis in patients from the age of 12 years
- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them
- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Enbrel

Do not use Enbrel

- if you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if you or the child have, or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child have an infection of any kind. If you are not sure, please talk to your doctor.

Warning and precautions

Talk to your doctor before taking Enbrel.

- **Allergic reactions**: If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Infections/surgery**: If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Enbrel. Treatment with Enbrel may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Enbrel.

- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.
- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Enbrel.
  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
  Children and adults taking Enbrel may have an increased risk of developing lymphoma or another cancer.
  Some children and teenage patients who have received Enbrel or other medicines that work the same way as Enbrel have developed cancers, including unusual types, which sometimes resulted in death.
  Some patients receiving Enbrel have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Enbrel. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Latex:** The needle cover is made from latex (dry natural rubber). Contact your doctor before using Enbrel if the needle cover will be handled by, or Enbrel will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Alcohol abuse**: Enbrel should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- **Wegener's granulomatosis**: Enbrel is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines**: Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Enbrel.

Children and adolescents

Vaccinations: If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult your doctor before you or the child receive any vaccines.

Enbrel should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

Other medicines and Enbrel

Tell your doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use Enbrel with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Enbrel should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Enbrel during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Enbrel in pregnancy, compared with mothers who had not received Enbrel or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Enbrel in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Enbrel during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines

The use of Enbrel is not expected to affect the ability to drive or use machines.

Enbrel contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to use Enbrel

Always use this medicine exactly as the doctor has told you. Check with the doctor or pharmacist if you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or pharmacist.

The pre-filled syringe is available in dose strengths of 25 mg and 50 mg.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Enbrel.

Plaque psoriasis

The usual dose is 25 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doctor will decide how long you should take Enbrel and whether retreatment is needed based on your response. If Enbrel has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of Enbrel (10 mg, 25 mg or 50 mg).

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Enbrel per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Enbrel per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of Enbrel per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Enbrel has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

Enbrel can be taken with or without food or drink.

Detailed instructions on how to inject Enbrel are provided in section 7, "Instructions for use."
Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Enbrel

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- **Signs of cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

The known side effects of Enbrel include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people):
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people):
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people):
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi’s sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi’s sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Additional side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enbrel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and pre-filled syringe after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2° – 8°C). Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light.

After taking a syringe from the refrigerator, **wait approximately 15-30 minutes to allow the Enbrel solution in the syringe to reach room temperature**. Do not warm in any other way. Immediate use is then recommended.

Enbrel may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that Enbrel is removed from the refrigerator and the date after which Enbrel should be discarded (no more than 4 weeks following the removal from the refrigerator).

Inspect the solution in the syringe. It should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enbrel contains

Enbrel 25 mg solution for injection in pre-filled syringe
The active substance in Enbrel is etanercept. Each pre-filled syringe contains 0.5 ml of solution, providing 25 mg of etanercept.

Enbrel 50 mg solution for injection in pre-filled syringe
The active substance in Enbrel is etanercept. Each pre-filled syringe contains 1.0 ml of solution, providing 50 mg of etanercept.

The other ingredients are sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate and sodium phosphate dibasic dihydrate, and water for injections.

What Enbrel looks like and contents of the pack

Enbrel 25 mg solution for injection in pre-filled syringe
Enbrel is supplied as a pre-filled syringe containing a clear, colourless to pale yellow or pale brown solution for injection (solution for injection). Each pack contains 4, 8, 12 or 24 pre-filled syringes and 4, 8, 12 or 24 alcohol swabs. Not all pack sizes may be marketed.

Enbrel 50 mg solution for injection in pre-filled syringe
Enbrel is supplied as a pre-filled syringe containing a clear, colourless to pale yellow or pale brown solution for injection (solution for injection). Each pack contains 2, 4 or 12 pre-filled syringes and 2, 4 or 12 alcohol swabs. Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

7. Instructions for use

This section is divided into the following subsections:

Introduction
Step 1: Setting up for an injection
Step 2: Choosing an injection site
Step 3: Injecting the Enbrel solution
Step 4: Disposing of supplies

Introduction

The following instructions explain how to prepare and inject Enbrel. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the techniques of self-injection or on giving an injection to a child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

The Enbrel solution should not be mixed with any other medicine before use.

Step 1: Setting up for an injection

1. Select a clean, well-lit, flat working surface.

2. Take the Enbrel carton containing the pre-filled syringes out of the refrigerator and place it on the flat work surface. Starting from one of the top corners, pull back the paper cover from the top and sides of the tray. Remove one pre-filled syringe and one alcohol swab and place them on the work surface. Do not shake the pre-filled syringe of Enbrel. Fold the paper cover back over the tray and place the carton containing any remaining pre-filled syringes back into the refrigerator. Please see section 5 for instructions on how to store Enbrel. If you have any questions about storage, contact your doctor, nurse, or pharmacist for further instructions.

3. **You should allow 15 to 30 minutes for the Enbrel solution in the syringe to reach room temperature. Do NOT** remove the needle cover while allowing it to reach room temperature. Waiting until the solution reaches room temperature may make the injection more comfortable for you. Do not warm Enbrel in any other way (for example, do not warm it in a microwave or in hot water).

4. Assemble the additional supplies you will need for your injection. These include the alcohol swab from the Enbrel carton and a cotton ball or gauze.

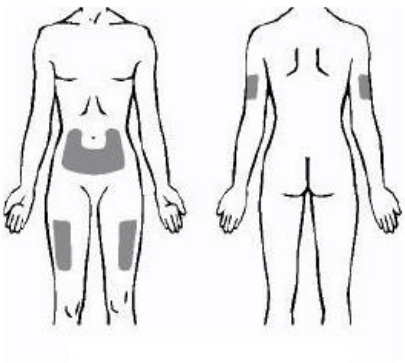
5. Wash your hands with soap and warm water.

6. Inspect the solution in the syringe. It should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Step 2: Choosing an injection site

1. The three recommended injection sites for Enbrel using a pre-filled syringe include: (1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right around the navel; and (3) the outer area of the upper arms (see Diagram 1). If you are self injecting, you should not use the outer area of the upper arms.

Diagram 1



2. A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)

3. If you or the child have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches (“psoriasis skin lesions”).

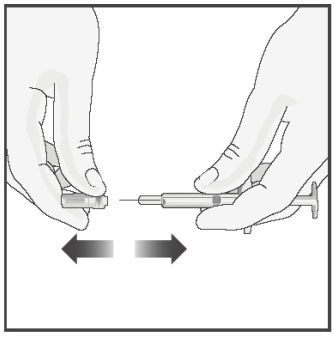
Step 3: Injecting the Enbrel solution

1. Wipe the site where Enbrel is to be injected with the alcohol swab, using a circular motion. **Do NOT** touch this area again before giving the injection.

2. Pick up the pre-filled syringe from the flat work surface. Remove the needle cover by firmly pulling it straight off the syringe (see Diagram 2). **Be careful not to bend or twist the cover during removal to avoid damage to the needle.**

   When you remove the needle cover, there may be a drop of liquid at the end of the needle; this is normal. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.

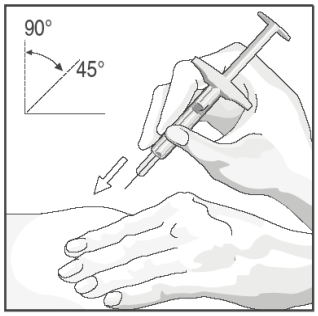
Diagram 2



3. When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.

4. With a quick, short motion, push the needle all the way into the skin at an angle between 45° and 90° (see Diagram 3). With experience, you will find the angle that is most comfortable for you or the child. Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 3



5. When the needle is completely inserted into the skin, release the skin that you are holding. With your free hand, hold the syringe near its base to stabilise it. Then push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 4).

Diagram 4



6. When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

Step 4: Disposing of supplies

- The pre-filled syringe is for single-use administration only. The syringe and needle should **NEVER** be re-used. **NEVER** re-cap a needle. Dispose of the needle and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with Enbrel.

Package leaflet: Information for the user

Enbrel 25 mg solution for injection in pre-filled pen
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

Information in this leaflet is organised under the following 7 sections:

1. What Enbrel is and what it is used for
2. What you need to know before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Contents of the pack and other information
7. Instructions for use

1. What Enbrel is and what it is used for

Enbrel is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Enbrel works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Enbrel can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis,** and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For rheumatoid arthritis, Enbrel is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Enbrel can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, Enbrel can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), Enbrel can slow down the structural damage to those joints caused by the disease.

Enbrel is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
    - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
    - Psoriatic arthritis in patients from the age of 12 years
- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them
- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Enbrel

Do not use Enbrel

- if you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if you or the child have, or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child have an infection of any kind. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Enbrel.

- **Allergic reactions:** If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Infections/surgery:** If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Enbrel. Treatment with Enbrel may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Enbrel.

- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.
- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Enbrel.
  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
  Children and adults taking Enbrel may have an increased risk of developing lymphoma or another cancer.
  Some children and teenage patients who have received Enbrel or other medicines that work the same way as Enbrel have developed cancers, including unusual types, which sometimes resulted in death.
  Some patients receiving Enbrel have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Enbrel. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Latex:** The needle cap of the MYCLIC pen is made from latex (dry natural rubber). Contact your doctor before using Enbrel if the needle cap will be handled by, or Enbrel will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Alcohol abuse:** Enbrel should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- **Wegener's granulomatosis:** Enbrel is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines:** Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Enbrel.

Children and adolescents

Vaccinations: If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult your doctor before you or the child receive any vaccines.

Enbrel should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

Other medicines and Enbrel

Tell your doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use Enbrel with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Enbrel should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Enbrel during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Enbrel in pregnancy, compared with mothers who had not received Enbrel or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Enbrel in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Enbrel during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines

The use of Enbrel is not expected to affect the ability to drive or use machines.

Enbrel contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to use Enbrel

Always use this medicine exactly as your doctor has told you. Check with your doctor if or pharmacist you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or pharmacist.

You have been prescribed a 25 mg strength of Enbrel. A 50 mg strength of Enbrel is available for doses of 50 mg.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Enbrel.

Plaque psoriasis

The usual dose is 25 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doctor will decide how long you should take Enbrel and whether retreatment is needed based on your response. If Enbrel has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of Enbrel (10 mg, 25 mg or 50 mg).

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Enbrel per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Enbrel per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of Enbrel per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Enbrel has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

Enbrel can be taken with or without food or drink.

Detailed instructions on how to inject Enbrel are provided in section 7, "Instructions for use."
Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Enbrel

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- **Signs of cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

The known side effects of Enbrel include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people):
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people):
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people):
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi’s sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi’s sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Additional side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enbrel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the MYCLIC pre-filled pen after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2° – 8°C). Do not freeze.
Keep the pre-filled pens in the outer carton in order to protect from light.

After taking a pre-filled pen from the refrigerator, **wait approximately 15-30 minutes to allow the Enbrel solution in the pen to reach room temperature**. Do not warm in any other way. Immediate use is then recommended.

Enbrel may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that Enbrel is removed from the refrigerator and the date after which Enbrel should be discarded (no more than 4 weeks following the removal from the refrigerator).

Inspect the solution in the pen by looking through the clear inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enbrel contains

The active substance in Enbrel is etanercept. Each MYCLIC pre-filled pen contains 25 mg of etanercept.

The other ingredients are sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate and sodium phosphate dibasic dihydrate, and water for injections.

What Enbrel looks like and contents of the pack

Enbrel is supplied as a solution for injection in a pre-filled pen (MYCLIC) (solution for injection). The MYCLIC pen contains a clear, colourless to pale yellow or pale brown solution for injection. Each pack contains 4, 8 or 24 pens and 4, 8 or 24 alcohol swabs. Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

7. Instructions for use

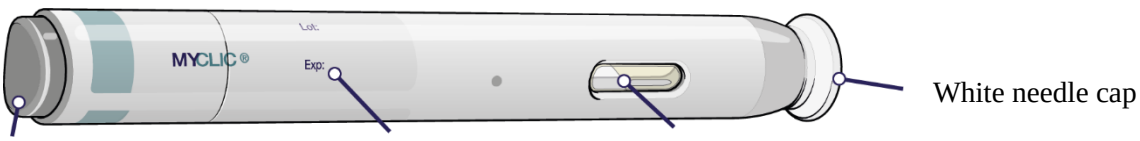
Enbrel 25 mg solution for injection in pre-filled pen
(etanercept)
For subcutaneous injection only

Introduction

- The instructions below explain how to use the MYCLIC pen to inject Enbrel.
- Please read the instructions carefully, and follow them step by step.
- Your healthcare provider will tell you how to inject Enbrel. Do not attempt to administer an injection until you are sure that you understand how to use the MYCLIC pen properly.
- If you have questions about how to inject, please ask your healthcare provider for help.

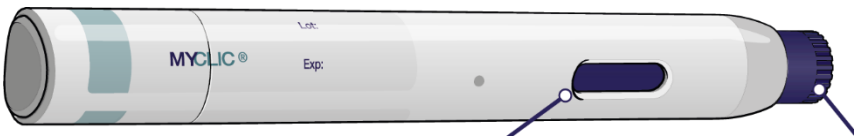
The MYCLIC pre-filled pen

Before injection



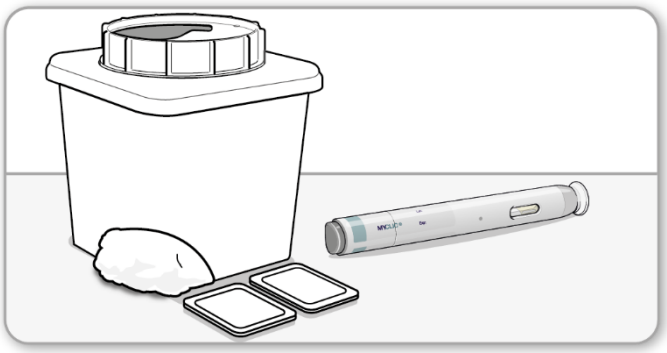
White needle cap
Grey activation button
Expiry date
Clear inspection window

After injection



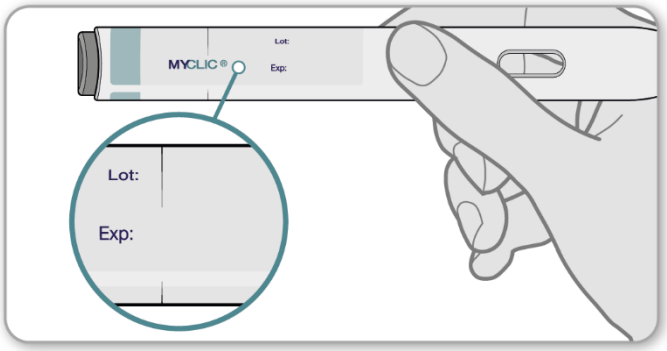
Filled inspection window
Open end – safety shield

Step 1 Preparing for an Enbrel injection



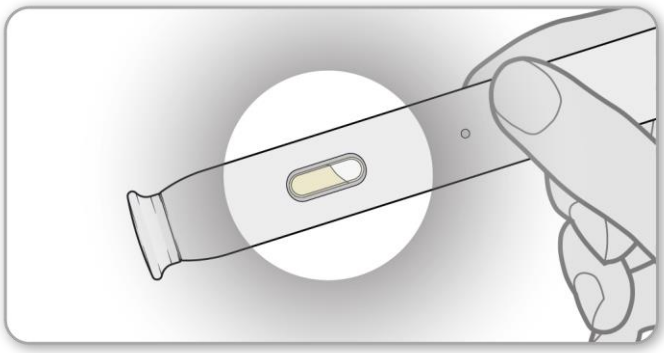
- **Gather** the following items for each injection on a clean, well-lit flat surface:
    - One MYCLIC pre-filled pen.
    - One alcohol swab.
    - A suitable sharps container (not included).
    - Clean cotton balls or gauze pads (not included).
- **Do not** shake the pen.
- **Do not** remove the white cap until instructed to do so.
- For a more comfortable injection, leave your pen at room temperature for 15 to 30 minutes with the white cap in place.
- **Do not** warm the pen in any other way.

Step 2 Check label for expiry and dose



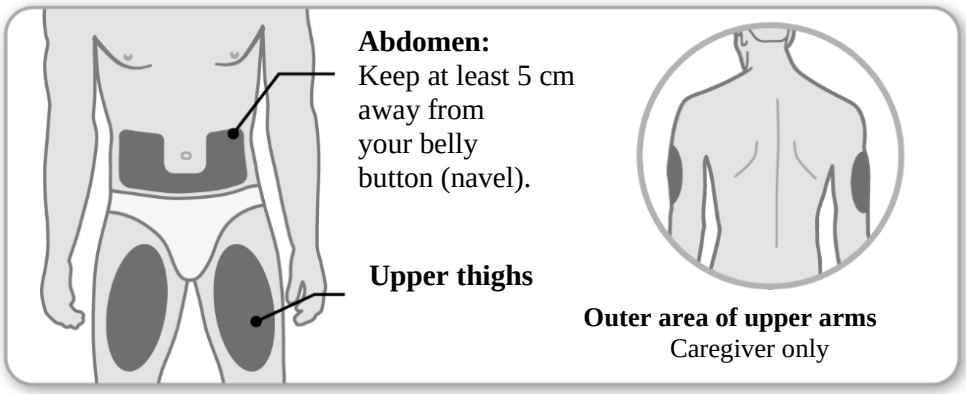
- **Check** the expiry date (month/year) on the pen label.
- **Make sure** the correct dose strength is shown on the pen label.
- If the expiry date has passed or it is not your prescribed dose, **do not** use the pen and contact your healthcare provider for assistance.

Step 3 Inspect the medicine



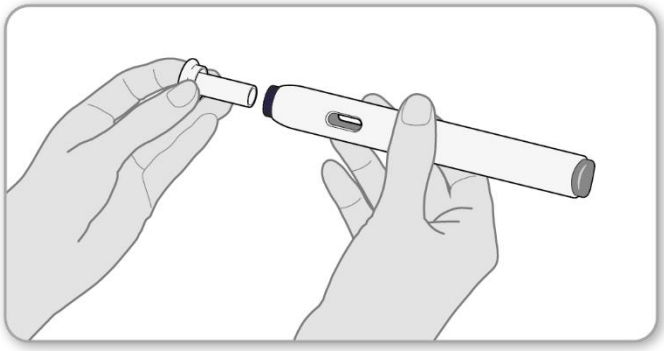
- **Inspect** the medicine in the pen by looking through the clear inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel.
- **Do not** use the medicine if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the medicine, then contact your healthcare provider for assistance.
- **Note:** You may see an air bubble in the window. This is normal.

Step 4 Choose and clean injection site



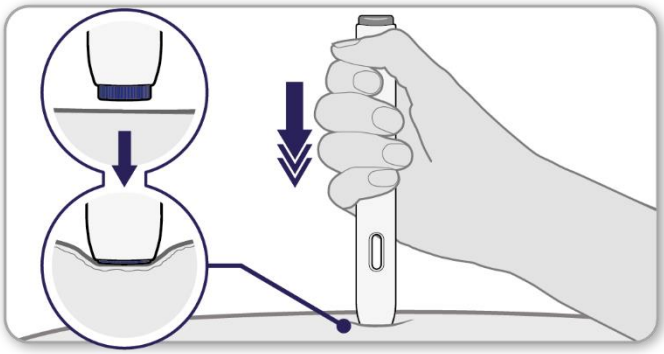
- **Choose** an injection site in the middle of the front of your upper thighs or stomach area 5 cm away from the belly button (navel). The outer area of the back of the upper arms may also be used by a caregiver.
- **Each** injection should be given at least 3 cm from where you last injected. **Do not** inject into tender, bruised or hard skin. Avoid scars or stretch marks. If you have psoriasis, **do not** inject directly into any raised, thick, red or scaly skin.
- **Clean** the injection site with soap and water, or an alcohol swab if convenient.
- **Allow** the site to dry. **Do not** touch, fan or blow on the cleaned injection site.

Step 5 Remove needle cap



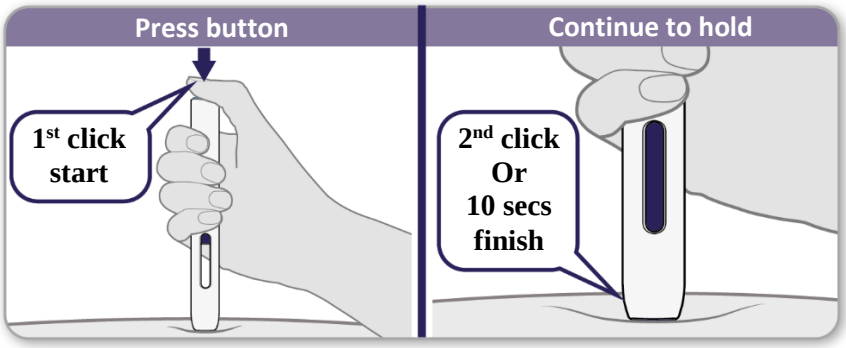
- **Remove** the white needle cap by pulling it straight off. **Do not** bend the cap while removing it.
- **Do not** re-attach the cap once it has been removed.
- After removal of the cap, you will see a purple needle safety shield extending slightly from the end of the pen. **Do not** push on the end safety shield with your fingers or thumbs.
- **Do not** use the pen if it is dropped with the needle cap off.
  Note: You may notice a drop of liquid at the needle tip. This is normal.

Step 6 Push pen firmly against skin



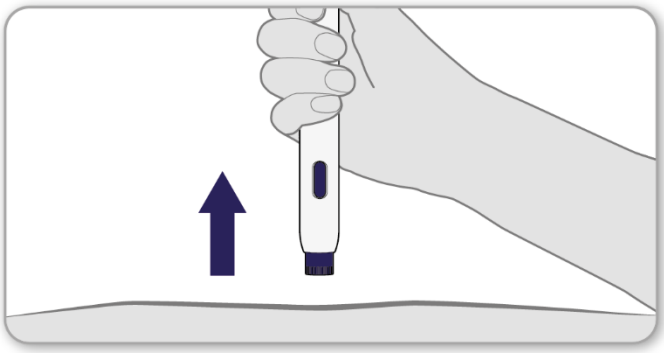
- **Push** the open end of your pen firmly against the skin at 90 degrees so the purple needle safety shield is pushed completely inside the pen.
  Note: You will only be able to press the grey button when the needle shield is completely pushed inside the pen.
  Pinching or stretching the skin before injection may make the injection site firmer, making it easier to press the injection button.

Step 7 Start your injection



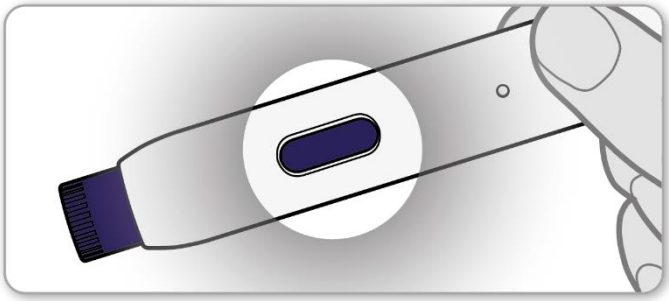
- **Press** the grey button all the way down and you will hear a **"click".** The click means the start of the injection.
- **Continue to hold** your pen firmly against the skin until you hear a **2nd "click"**, or until 10 seconds after the first click (whichever happens first).
  Note: If you are unable to start the injection as described, press the pen more firmly against your skin, then press the grey button again.

Step 8 Lift off skin



- **Remove** your pen from your skin by lifting it straight off the injection site.
- The purple needle safety shield will automatically extend to cover the needle.

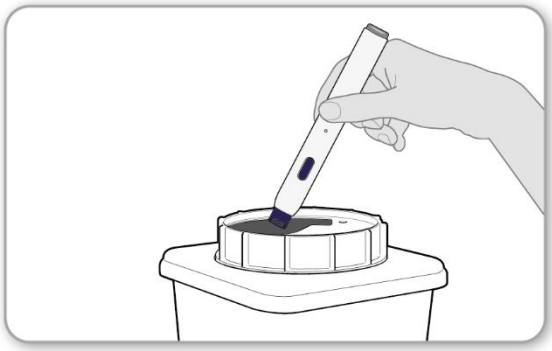
Step 9 Check inspection window



- **Check** the pen's inspection window. It should be completely purple.
- If the window is not purple, you may not have received a full dose. Contact your healthcare provider for assistance. **Do not** try to use the pen again. **Do not** try to use another pen.
- If you notice a spot of blood at the injection site you should press the cotton ball or gauze over the injection site for 10 seconds. **Do not** rub the injection site.

Note: The injection button may stay pressed in. This is normal.

Step 10 Dispose



- **Dispose** of the used pen as instructed by your healthcare provider. **Do not** attempt to recap the pen.
- **Do not** press on the end of the needle safety shield. If you have any questions, please talk to your healthcare provider.

--End of Instructions for Use—

Package leaflet: Information for the user

Enbrel 50 mg solution for injection in pre-filled pen
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

Information in this leaflet is organised under the following 7 sections:

1. What Enbrel is and what it is used for
2. What you need to know before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Contents of the pack and other information
7. Instructions for use

1. What Enbrel is and what it is used for

Enbrel is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Enbrel works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Enbrel can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis,** and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For rheumatoid arthritis, Enbrel is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Enbrel can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, Enbrel can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), Enbrel can slow down the structural damage to those joints caused by the disease.

Enbrel is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
    - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
    - Psoriatic arthritis in patients from the age of 12 years
- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them
- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Enbrel

Do not use Enbrel

- if you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if you or the child have, or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child have an infection of any kind. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Enbrel.

- **Allergic reactions:** If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Infections/surgery:** If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Enbrel. Treatment with Enbrel may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Enbrel.

- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.
- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Enbrel.
  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
  Children and adults taking Enbrel may have an increased risk of developing lymphoma or another cancer.
  Some children and teenage patients who have received Enbrel or other medicines that work the same way as Enbrel have developed cancers, including unusual types, which sometimes resulted in death.
  Some patients receiving Enbrel have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Enbrel. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Latex:** The needle cap of the MYCLIC pen is made from latex (dry natural rubber). Contact your doctor before using Enbrel if the needle cap will be handled by, or Enbrel will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Alcohol abuse:** Enbrel should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- **Wegener's granulomatosis:** Enbrel is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines:** Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Enbrel.

Children and adolescents

Vaccinations: If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult your doctor before you or the child receive any vaccines.

Enbrel should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

Other medicines and Enbrel

Tell your doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use Enbrel with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Enbrel should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Enbrel during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Enbrel in pregnancy, compared with mothers who had not received Enbrel or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Enbrel in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Enbrel during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines

The use of Enbrel is not expected to affect the ability to drive or use machines.

Enbrel contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to use Enbrel

Always use this medicine exactly as your doctor has told you. Check with your doctor if or pharmacist you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or pharmacist.

You have been prescribed a 50 mg strength of Enbrel. A 25 mg strength of Enbrel is available for doses of 25 mg.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Enbrel.

Plaque psoriasis

The usual dose is 25 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doctor will decide how long you should take Enbrel and whether retreatment is needed based on your response. If Enbrel has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of Enbrel (10 mg, 25 mg or 50 mg).

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Enbrel per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Enbrel per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of Enbrel per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Enbrel has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

Enbrel can be taken with or without food or drink.

Detailed instructions on how to inject Enbrel are provided in section 7 "Instructions for use". Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Enbrel

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- **Signs of cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

The known side effects of Enbrel include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people):
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people):
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people):
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi’s sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi’s sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Additional side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enbrel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the MYCLIC pre-filled pen after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2° – 8°C). Do not freeze.
Keep the pre-filled pens in the outer carton in order to protect from light.

After taking a pre-filled pen from the refrigerator, **wait approximately 15-30 minutes to allow the Enbrel solution in the pen to reach room temperature**. Do not warm in any other way. Immediate use is then recommended.

Enbrel may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that Enbrel is removed from the refrigerator and the date after which Enbrel should be discarded (no more than 4 weeks following the removal from the refrigerator).

Inspect the solution in the pen by looking through the clear inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enbrel contains

The active substance in Enbrel is etanercept. Each MYCLIC pre-filled pen contains 50 mg of etanercept.

The other ingredients are sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate and sodium phosphate dibasic dihydrate, and water for injections.

What Enbrel looks like and contents of the pack

Enbrel is supplied as a solution for injection in a pre-filled pen (MYCLIC) (solution for injection). The MYCLIC pen contains a clear, colourless to pale yellow or pale brown solution for injection. Each pack contains 2, 4 or 12 pens and 2, 4 or 12 alcohol swabs. Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

7. Instructions for use

Enbrel 50 mg solution for injection in pre-filled pen
(etanercept)
For subcutaneous injection only

Introduction

- The instructions below explain how to use the MYCLIC pen to inject Enbrel.
- Please read the instructions carefully, and follow them step by step.
- Your healthcare provider will tell you how to inject Enbrel. Do not attempt to administer an injection until you are sure that you understand how to use the MYCLIC pen properly.
- If you have questions about how to inject, please ask your healthcare provider for help.

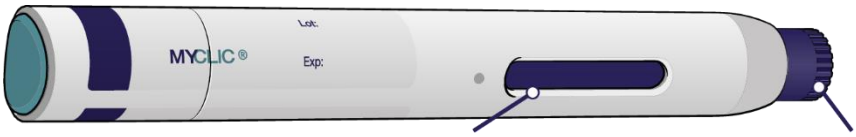
The MYCLIC pre-filled pen

Before injection



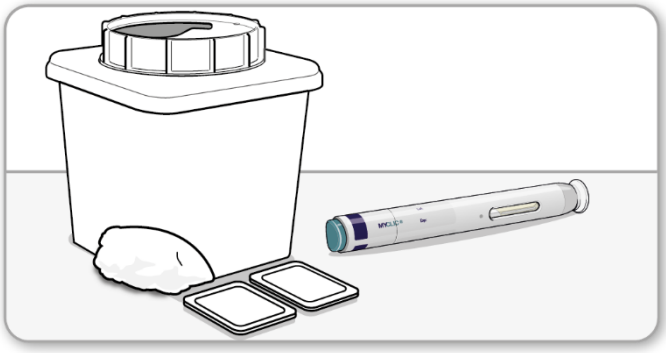
White needle cap
Green activation button
Expiry date
Clear inspection window

After injection



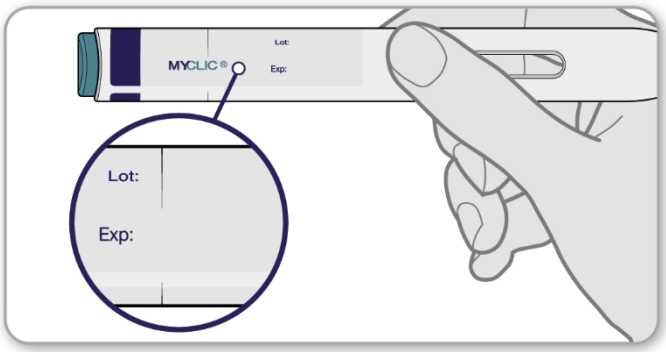
Filled inspection window
Open end – safety shield

Step 1 Preparing for an Enbrel injection



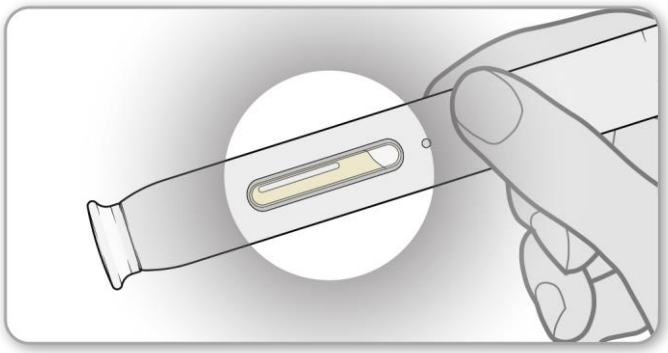
- **Gather** the following items for each injection on a clean, well-lit flat surface:
  - One MYCLIC pre-filled pen.
  - One alcohol swab.
  - A suitable sharps container (not included).
  - Clean cotton balls or gauze pads (not included).
- **Do not** shake the pen.
- **Do not** remove the white cap until instructed to do so.
- For a more comfortable injection, leave your pen at room temperature for 15 to 30 minutes with the white cap in place.
- **Do not** warm the pen in any other way.

Step 2 Check label for expiry and dose



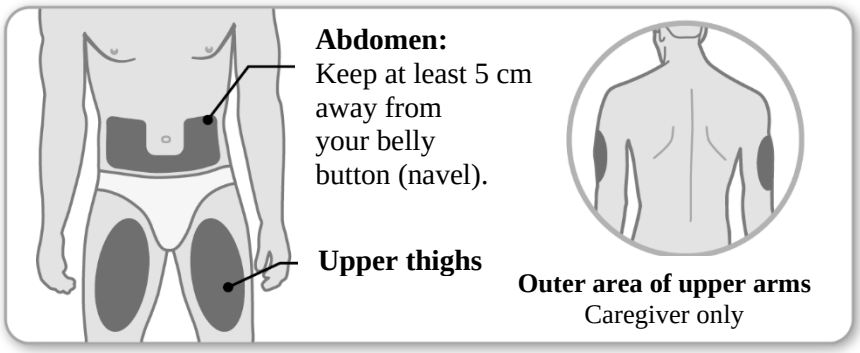
- **Check** the expiry date (month/year) on the pen label.
- **Make sure** the correct dose strength is shown on the pen label.
- If the expiry date has passed or it is not your prescribed dose, **do not** use the pen and contact your healthcare provider for assistance.

Step 3 Inspect the medicine



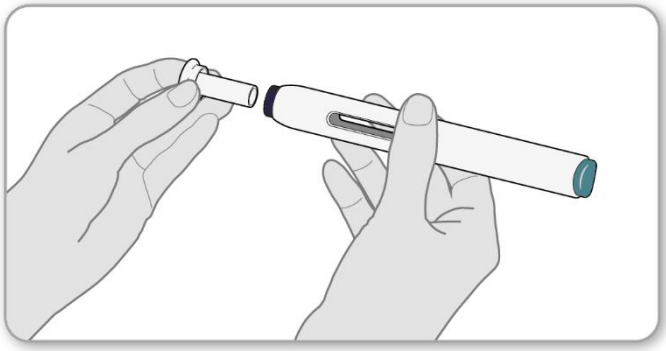
- **Inspect** the medicine in the pen by looking through the clear inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel.
- **Do not** use the medicine if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the medicine, then contact your healthcare provider for assistance.
- **Note:** You may see an air bubble in the window. This is normal.

Step 4 Choose and clean injection site



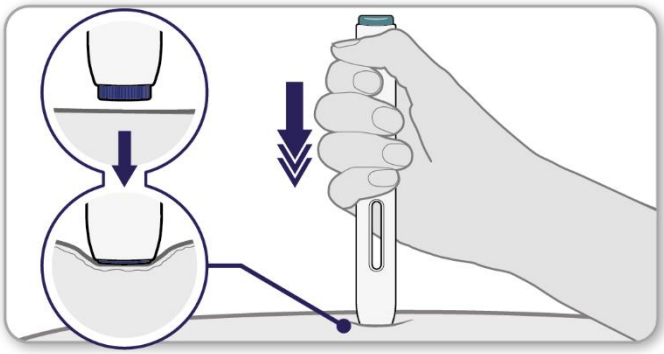
- **Choose** an injection site in the middle of the front of your upper thighs or stomach area 5 cm away from the belly button (navel). The outer area of the back of the upper arms may also be used by a caregiver.
- **Each** injection should be given at least 3 cm from where you last injected. **Do not** inject into tender, bruised or hard skin. Avoid scars or stretch marks. If you have psoriasis, **do not** inject directly into any raised, thick, red or scaly skin.
- **Clean** the injection site with soap and water, or an alcohol swab if convenient.
- **Allow** the site to dry. **Do not** touch, fan or blow on the cleaned injection site.

Step 5 Remove needle cap



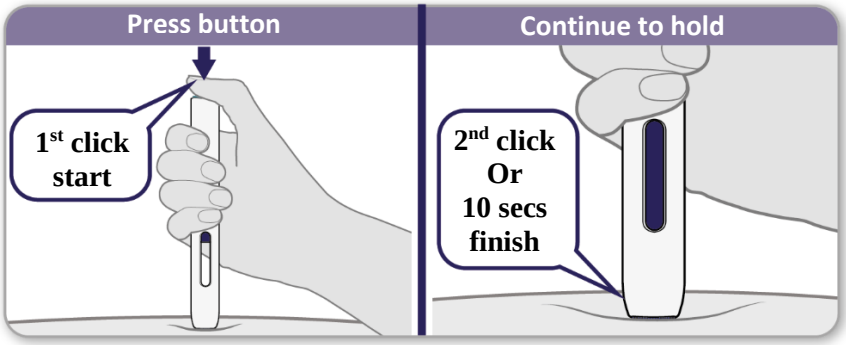
- **Remove** the white needle cap by pulling it straight off. **Do not** bend the cap while removing it.
- **Do not** re-attach the cap once it has been removed.
- After removal of the cap, you will see a purple needle safety shield extending slightly from the end of the pen. **Do not** push on the end safety shield with your fingers or thumbs.
- **Do not** use the pen if it is dropped with the needle cap off.
  Note: You may notice a drop of liquid at the needle tip. This is normal.

Step 6 Push pen firmly against skin



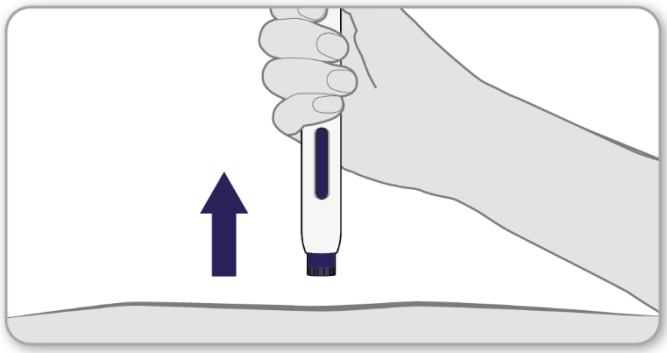
- **Push** the open end of your pen firmly against the skin at 90 degrees so the purple needle safety shield is pushed completely inside the pen.
  Note: You will only be able to press the green button when the needle shield is completely pushed inside the pen.
  Pinching or stretching the skin before injection may make the injection site firmer, making it easier to press the injection button.

Step 7 Start your injection



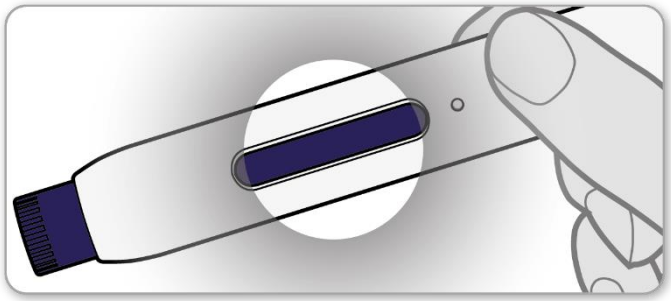
- **Press** the green button all the way down and you will hear a **"click".** The click means the start of the injection.
- **Continue to hold** your pen firmly against the skin until you hear a **2nd "click"**, or until 10 seconds after the first click (whichever happens first).
  Note: If you are unable to start the injection as described, press the pen more firmly against your skin, then press the green button again.

Step 8 Lift off skin



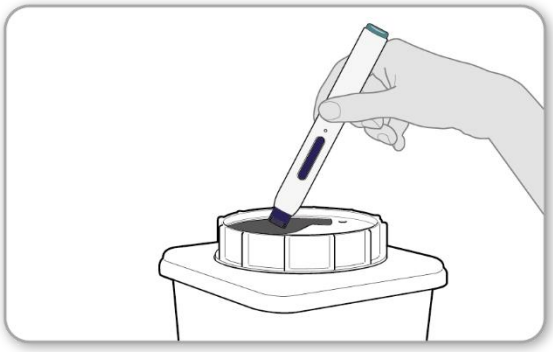
- **Remove** your pen from your skin by lifting it straight off the injection site.
- The purple needle safety shield will automatically extend to cover the needle.

Step 9 Check inspection window



- **Check** the pen's inspection window. It should be completely purple.
- If the window is not purple, you may not have received a full dose. Contact your healthcare provider for assistance. **Do not** try to use the pen again. **Do not** try to use another pen.
- If you notice a spot of blood at the injection site you should press the cotton ball or gauze over the injection site for 10 seconds. **Do not** rub the injection site.
  Note: The injection button may stay pressed in. This is normal.

Step 10 Dispose



- **Dispose** of the used pen as instructed by your healthcare provider. **Do not** attempt to recap the pen.
- **Do not** press on the end of the needle safety shield. If you have any questions, please talk to your healthcare provider.

--End of Instructions for Use—

Package leaflet: Information for the user

Enbrel 10 mg powder and solvent for solution for injection for paediatric use
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

Information in this leaflet is organised under the following 7 sections:

1. What Enbrel is and what it is used for
2. What you need to know before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Contents of the pack and other information
7. Instructions for use

1. What Enbrel is and what it is used for

Enbrel is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Enbrel works by reducing the inflammation associated with certain diseases.

Enbrel is prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
    - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
    - Psoriatic arthritis in patients from the age of 12 years
- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them
- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Enbrel

Do not use Enbrel

- if the child you are caring for is allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If the child experiences allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if the child has, or is at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if the child has an infection of any kind. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Enbrel.

- **Allergic reactions:** If the child experiences allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Latex:** The syringe rubber tip is made from latex (dry natural rubber). Contact your doctor before using Enbrel if the syringe will be handled by, or Enbrel will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Infections/surgery:** If the child develops a new infection, or is about to have any major surgery, the doctor may wish to monitor the child's treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if the child has a history of recurrent infections, or suffers from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If the child develops symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor the child for the presence of infections after the child stops using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if the child has ever had tuberculosis, or has been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if the child has or has ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before the child begins treatment with Enbrel. Treatment with Enbrel may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Enbrel.
- **Hepatitis C:** Tell your doctor if the child has hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if the child has any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.
- **Nervous system and eye disorders:** Tell your doctor if the child has multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if the child has a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if the child has or has ever had lymphoma (a type of blood cancer) or any other cancer before the child is given Enbrel.
  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.

Children and adults taking Enbrel may have an increased risk of developing lymphoma or another cancer.
Some children and teenage patients who have received Enbrel or other medicines that work the same way as Enbrel have developed cancers, including unusual types, which sometimes resulted in death.
Some patients receiving Enbrel have developed skin cancers. Tell your doctor if the child develops any change in the appearance of the skin or growths on the skin.

- **Chickenpox:** Tell your doctor if the child is exposed to chickenpox when using Enbrel. Your doctor will determine if preventative treatment for chickenpox is appropriate.
- **Alcohol abuse:** Enbrel should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if the child in your care has a history of alcohol abuse.
- **Wegener's granulomatosis:** Enbrel is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If the child in your care has Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines:** Tell your doctor if the child has diabetes or is taking medicines to treat diabetes. Your doctor may decide if the child needs less anti-diabetic medicine while taking Enbrel.

Children and adolescents

Vaccinations: If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult the child's doctor before the child receives any vaccines.

Enbrel should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

Other medicines and Enbrel

Tell your doctor or pharmacist if the child is taking, has recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the child's doctor. The child should not use Enbrel with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Enbrel should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Enbrel during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Enbrel in pregnancy, compared with mothers who had not received Enbrel or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Enbrel in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Enbrel during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines

The use of Enbrel is not expected to affect the ability to drive or use machines.

3. How to use Enbrel

Use in children and adolescents

Always use this medicine exactly as the doctor has told you. Check with the doctor or pharmacist if you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or pharmacist.

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

The 10 mg vial is for children prescribed a dose of 10 mg or less. Each vial should be used for just one dose in one patient, and any remaining solution should be discarded.

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Enbrel per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Enbrel per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of Enbrel per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Enbrel has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

Enbrel can be taken with or without food or drink.

The powder must be dissolved before use. **Detailed instructions on how to prepare and inject Enbrel are provided in section 7, "Instructions for use".** Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Enbrel

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen to the child, do not give the child more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. If the child has any of the above symptoms he/she may be having an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- **Signs of cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or take the child to the casualty department at your nearest hospital.

The known side effects of Enbrel include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people):
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people):
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people):
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi’s sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi’s sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Additional side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enbrel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Before preparing the Enbrel solution, Enbrel may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that Enbrel is removed from the refrigerator and the date after which Enbrel should be discarded (no more than 4 weeks following the removal from the refrigerator). This new expiry date should not exceed the expiry date recorded on the outer carton.

After preparing the Enbrel solution, immediate use is recommended. However, the solution may be used for up to 6 hours when stored at a temperature up to 25°C.

Do not use this medicine if you notice the solution is not clear or contains particles. The solution should be clear, colourless to pale yellow or pale brown, with no lumps or flakes or particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enbrel contains

The active ingredient in Enbrel is etanercept. Each vial of Enbrel 10 mg powder and solvent for solution for injection for paediatric use contains 10 mg of etanercept. When reconstituted, the solution contains 10 mg/ml of etanercept.

The other ingredients are:
Powder: Mannitol (E421), sucrose, and trometamol.
Solvent: Water for injections.

What Enbrel looks like and contents of the pack

Enbrel 10 mg powder and solvent for solution for injection for paediatric use is supplied as a white powder with solvent for solution for injection (powder for injection). Each pack contains 4 vials, 4 pre-filled syringes of water for injections, 4 needles, 4 vial adaptors and 8 alcohol swabs.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

7. Instructions for use

This section is divided into the following sub-sections:

a. Introduction
b. Setting up for an injection
c. Preparing the Enbrel dose for injection
d. Adding solvent
e. Withdrawing the Enbrel solution from the vial
f. Placing the needle on the syringe
g. Choosing an injection site
h. Preparing the injection site and injecting the Enbrel solution
i. Disposing of supplies

a. Introduction

The following instructions explain how to prepare and inject Enbrel. Please read the instructions carefully and follow them step by step. You will be instructed by the child's doctor or his/her assistant on the technique of giving an injection and on the amount to be given to the child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

This injection should not be mixed in the same syringe or vial with any other medicine. See section 5 for instructions on how to store Enbrel.

b. Setting up for an injection

- Wash your hands thoroughly.
- Select a clean well-lit, flat working surface.
- The dose tray should contain the items listed below. (If not, don't use the dose tray and consult your pharmacist). Use only the items listed. **Do NOT** use any other syringe.
  1 Enbrel vial
  1 Pre-filled syringe containing clear, colourless solvent (water for injections)
  1 Needle
  1 Vial adaptor
  2 Alcohol swabs
- Inspect the expiry dates on both the vial label and the syringe label. They should not be used after the month and year shown.

c. Preparing the Enbrel dose for injection

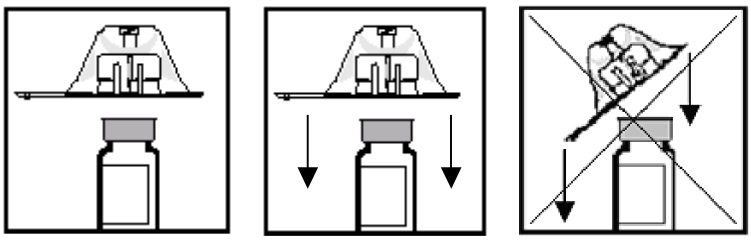
- Remove the contents of the tray
- Remove the plastic cap from the Enbrel vial (see Diagram 1). **Do NOT** remove the grey stopper or aluminium ring around the top of the vial.

Diagram 1



- Use a new alcohol swab to clean the grey stopper on the Enbrel vial. After cleaning, do not touch the stopper with your hands or allow it to touch any surface.
- Place the vial upright on a clean, flat surface.
- Remove the paper backing from the vial adaptor package.
- While still in the plastic package, place the vial adaptor on top of the Enbrel vial so that the vial adaptor spike is centered within the raised circle on top of the vial stopper (see Diagram 2).
- Hold the vial firmly on the flat surface with one hand. With the other hand, push **STRAIGHT DOWN FIRMLY** on the adaptor package until you feel the adaptor spike penetrate the vial stopper and **FEEL AND HEAR THE ADAPTOR RIM LOCK INTO PLACE** (see Diagram 3). **Do NOT** push down the adaptor at an angle (see Diagram 4). It is important that the vial adaptor spike completely penetrates the vial stopper.

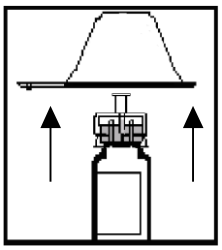
Diagram 2 Diagram 3 Diagram 4



CORRECT **INCORRECT**

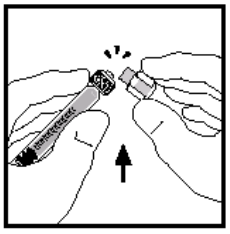
- While holding the vial in one hand, remove the plastic packaging from the vial adaptor (see Diagram 5).

Diagram 5



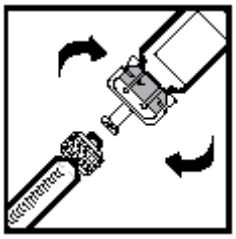
- Remove the protective cover from the syringe tip by breaking the white cap along the perforation. This is done by holding the collar of the white cap while grasping the end of the white cap with the other hand and bending it down and then up until it is broken (see Diagram 6). **Do NOT remove the white collar that remains on the syringe**.

Diagram 6



- Do not use the syringe if the perforation between the tip and collar is already broken. Start again with another dose tray.
- Holding the glass barrel of the syringe (not the white collar) in one hand, and the vial adaptor (not the vial) in the other, connect the syringe to the vial adaptor by inserting the tip into the opening and turn clockwise until completely secured (see Diagram 7).

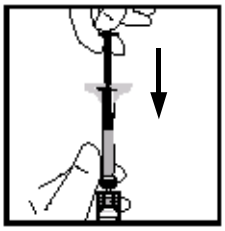
Diagram 7



d. Adding solvent

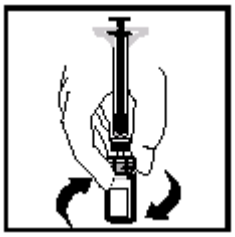
- While holding the vial upright on the flat surface, push the plunger VERY SLOWLY until all the solvent is in the vial. This will help to reduce foaming (lots of bubbles) (see Diagram 8).
- Once the solvent is added to the Enbrel, the plunger may move up by itself. This is due to air pressure and should not be of concern.

Diagram 8



- With the syringe still attached, gently move the vial in circles a few times, to dissolve the powder (see Diagram 9). **Do NOT** shake the vial. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes, or particles. Some white foam may remain in the vial this is normal. **Do NOT** use Enbrel if all the powder in the vial is not dissolved within 10 minutes. Start again with another dose tray.

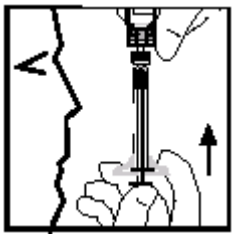
Diagram 9



e. Withdrawing the Enbrel solution from the vial

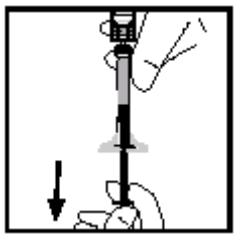
- The doctor or his/her assistant should have instructed you on the proper amount of solution to be withdrawn from the vial. If the doctor has not given this instruction, please contact him/her.
- With the syringe still attached to the vial and vial adaptor, hold the vial upside down at eye level. Push the plunger all the way into the syringe (see Diagram 10).

Diagram 10



- Then, slowly pull the plunger back to draw the liquid into the syringe (see Diagram 11). Remove only the portion of liquid as directed by your child's doctor. After you have withdrawn the Enbrel from the vial, you may have some air in the syringe. Do not be concerned, as you will remove the air in a later step.

Diagram 11



- With the vial held upside down, unscrew the syringe from the vial adaptor by turning it anti-clockwise (see Diagram 12).

Diagram 12



- Place the filled syringe on the clean, flat surface. Make sure that the tip does not touch anything. Be careful not to push down on the plunger.

f. Placing the needle on the syringe

- The needle has been placed in a plastic container to keep it sterile.
- To open the plastic container, hold the short, wide end in one hand. Place your other hand on the longer portion of the container.
- To break the seal, bend the larger end down and then up until broken (see Diagram 13).

Diagram 13



- Once the seal has been broken, remove the short, wide end of the plastic container.
- The needle will remain in the long part of the package.
- While holding the needle and container in one hand, pick up the syringe and insert the syringe tip into the needle opening.
- Attach the syringe to the needle by turning it clockwise until completely secured (see Diagram 14).

Diagram 14



- Remove the needle cover by firmly pulling it straight off the syringe taking care not to touch the needle or allow the needle to touch any surfaces (see Diagram 15). Be careful not to bend or twist the cover during removal to avoid damage to the needle.

Diagram 15



- While holding the syringe upright, remove any air bubbles by slowly pushing on the plunger until the air is removed (see Diagram 16).

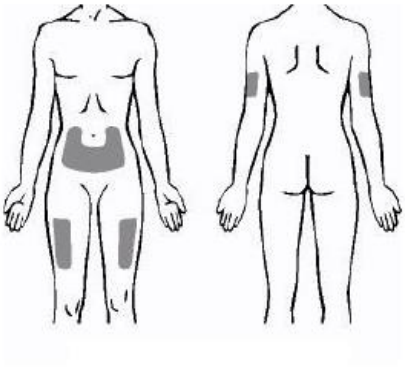
Diagram 16



g. Choosing an injection site

- The three recommended injection sites for Enbrel include: (1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right around the navel; and (3) the outer area of the upper arms (see Diagram 17). If you are self injecting, you should not use the outer area of the upper arms.

Diagram 17

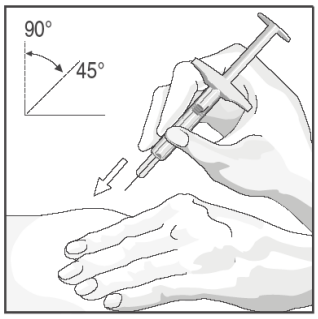


- A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. **Do NOT** inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
- If the child has psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skin lesions").

h. Preparing the injection site and injecting the Enbrel solution

- Wipe the site where Enbrel is to be injected with a new alcohol swab, using a circular motion. **Do NOT** touch this area again before giving the injection.
- When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
- With a quick, short motion, push the needle all the way into the skin at an angle between 45° and 90° (see Diagram 18). With experience, you will find the angle that is most comfortable for the child. Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 18



- When the needle is completely inserted into the skin, release the skin that you are holding. With your free hand, hold the syringe near its base to stabilise it. Then push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 19).

Diagram 19



- When the syringe is empty, remove the needle from the skin; being careful to keep it at the same angle it was when it was inserted.
- Press a cotton ball over the injection site for 10 seconds. Slight bleeding may occur. **Do NOT** rub the injection site. A bandage is optional.

i. Disposing of supplies

- The syringe and needles should **NEVER** be re-used. Dispose of the needles and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with Enbrel.

Package leaflet: Information for the user

Enbrel 25 mg solution for injection in dose-dispenser cartridge
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

Information in this leaflet is organised under the following 6 sections:

1. What Enbrel is and what it is used for
2. What you need to know before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Contents of the pack and other information (See Instructions for use)

1. What Enbrel is and what it is used for

Enbrel is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Enbrel works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Enbrel can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis,** and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For rheumatoid arthritis, Enbrel is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Enbrel can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, Enbrel can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), Enbrel can slow down the structural damage to those joints caused by the disease.

Enbrel is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
    - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years

- Psoriatic arthritis in patients from the age of 12 years

- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them

- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Enbrel

Do not use Enbrel

- if you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if you or the child have, or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child, have an infection of any kind. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Enbrel.

- **Allergic reactions:** If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Infections/surgery:** If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Enbrel. Treatment with Enbrel may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Enbrel.
- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.

- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Enbrel.
  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
  Children and adults taking Enbrel may have an increased risk of developing lymphoma or another cancer.
  Some children and teenage patients who have received Enbrel or other medicines that work the same way as Enbrel have developed cancers, including unusual types, which sometimes resulted in death.
  Some patients receiving Enbrel have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Enbrel. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Latex:** The needle cover is made from latex (dry natural rubber). Contact your doctor before using Enbrel if the needle cover will be handled by, or Enbrel will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Alcohol abuse:** Enbrel should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- **Wegener's granulomatosis:** Enbrel is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines:** Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Enbrel.

Children and adolescents

Vaccinations: If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult the child's doctor before the child receives any vaccines.

Enbrel should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

Other medicines and Enbrel

Tell the doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use Enbrel with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Enbrel should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Enbrel during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Enbrel in pregnancy, compared with mothers who had not received Enbrel or other similar medicines (TNF-antagonists),

but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Enbrel in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Enbrel during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines

The use of Enbrel is not expected to affect the ability to drive or use machines.

Enbrel contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to use Enbrel

Always use this medicine exactly as the doctor has told you. Check with the doctor or pharmacist if you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or pharmacist.

The dose-dispenser cartridge is available in dose strengths of 25 mg and 50 mg.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Enbrel.

Plaque psoriasis

The usual dose is 25 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doctor will decide how long you should take Enbrel and whether retreatment is needed based on your response. If Enbrel has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of Enbrel (10 mg, 25 mg or 50 mg).

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Enbrel per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Enbrel per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of Enbrel per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Enbrel has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

Enbrel can be taken with or without food or drink.

Detailed instructions on how to inject Enbrel are provided in "Instructions for use". Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Enbrel

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- **Signs of cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

The known side effects of Enbrel include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people):
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people):
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people):
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to

those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi's sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enbrel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the dose-dispenser cartridge in the outer carton in order to protect from light.

After taking a dose-dispenser cartridge from the refrigerator, wait approximately 15-30 minutes to allow the Enbrel solution in the dose-dispenser cartridge to reach room temperature. Do not warm in any other way. Immediate use is then recommended.

The dose-dispenser cartridges may be stored at room temperature (up to 25°C) for a single period of up to 4 weeks with protection from light; after which they should not be refrigerated again. Enbrel should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that the Enbrel dose-dispenser is removed from the refrigerator and the date after which Enbrel should be discarded (no more than 4 weeks following the removal from the refrigerator).

Inspect the solution in the dose-dispenser cartridge by looking through the inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enbrel contains

Enbrel 25 mg solution for injection in dose-dispenser cartridge
The active substance in Enbrel is etanercept. Each dose-dispenser cartridge contains 0.5 ml of solution, providing 25 mg of etanercept.

The other ingredients are sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate and sodium phosphate dibasic dihydrate, and water for injections.

What Enbrel looks like and contents of the pack

Enbrel is provided as a solution for injection in a ready to use dose-dispenser cartridge. The dose-dispenser cartridge is to be used with SMARTCLIC device. The device is provided separately. The solution is clear to opalescent, colourless to pale yellow or pale brown.

Enbrel 25 mg solution for injection in dose-dispenser cartridge
Cartons contain 4, 8 or 24 dose-dispenser cartridges with 8, 16 or 48 alcohol swabs. Not all pack sizes may be marketed.

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Manufacturer
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Instructions for use
Enbrel
(etanercept)
25 mg / 0.5 ml
For Subcutaneous Injection Only

Important Information

- Keep this Instructions for use, it shows step-by-step how to prepare and give an injection.
- Only use Enbrel after you read and understand this Instructions for use.
- Only use Enbrel after you have received training from your healthcare professional.
- Your Dose Dispenser Cartridge contains a single dose of Enbrel and must only be used with your SMARTCLIC Device.
- Dose Dispenser Cartridge and SMARTCLIC Device will be referred to as "Cartridge" and "Device" in this Instructions for use.
- If this is the first time you are using your Device, make sure you follow the setup instructions in the separate User Manual. You will not be able to use your Device until you complete the setup.
- **Do not** attempt to use your Cartridges with any other Device.
- **Do not** share your Cartridges or your Device with another person.
- **Do not** shake your Cartridges or your Device containing a Cartridge.
- **Do not** remove your Cartridge needle cap until instructed to do so.
- **Do not** reuse your Cartridge if the needle cap has been removed.
- Avoid spilling liquid on your Cartridges or your Device. Never rinse or put your Cartridges or your Device under water.
- Refer to the additional Device User Manual for accessing menus, using a Training Cartridge, advanced use and troubleshooting error messages.

Storage

- Store Cartridges in the refrigerator between 2 ºC to 8 ºC. **Do not** freeze your Cartridges. **Do not** store your Cartridges in your Device.
- Store Cartridges in their original Carton until use to protect from direct sunlight.
- You may store your Cartridges at room temperature up to 25 ºC for up to 4 weeks. **Do not** return them to the refrigerator after they have reached room temperature.
- Keep your Cartridges and your Device out of sight and reach of children and adolescents.
- Refer to your Device User Manual for how to store and clean your Device.

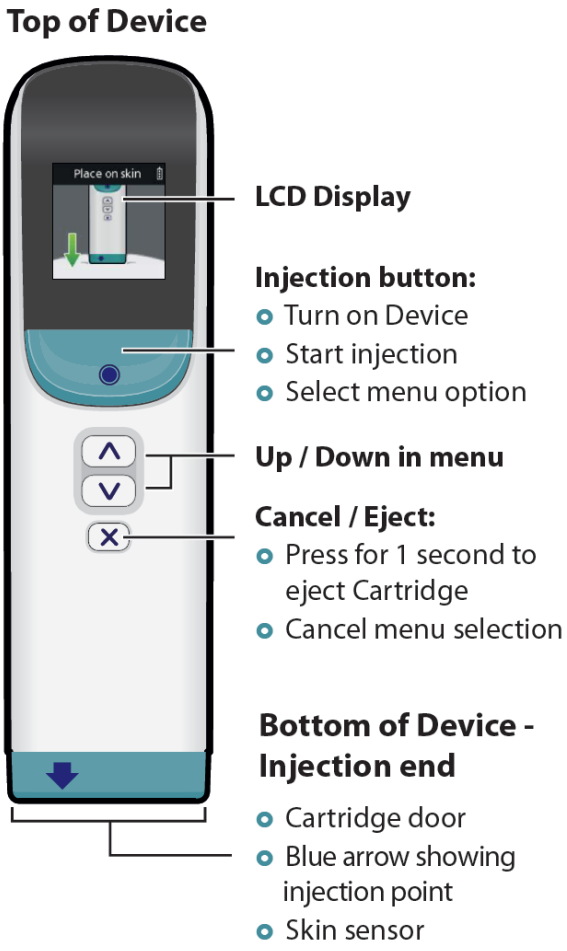
Supplies you need

- **Gather** the following supplies on a clean flat surface:
    - Enbrel Carton containing Cartridges
    - your SMARTCLIC Device
    - alcohol wipes
    - clean cotton balls or gauze pads (not included)
    - a suitable sharps container (not included).

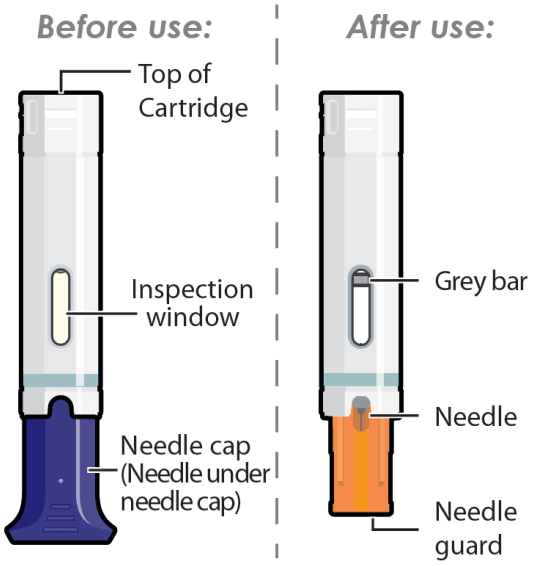
- **Do not** use if the Carton is dropped or damaged.
  Note: If you do not have everything you need, ask your healthcare professional.

Your Device:

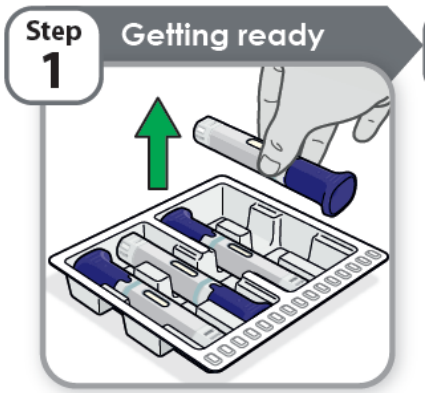
Refer to User Manual for more information.



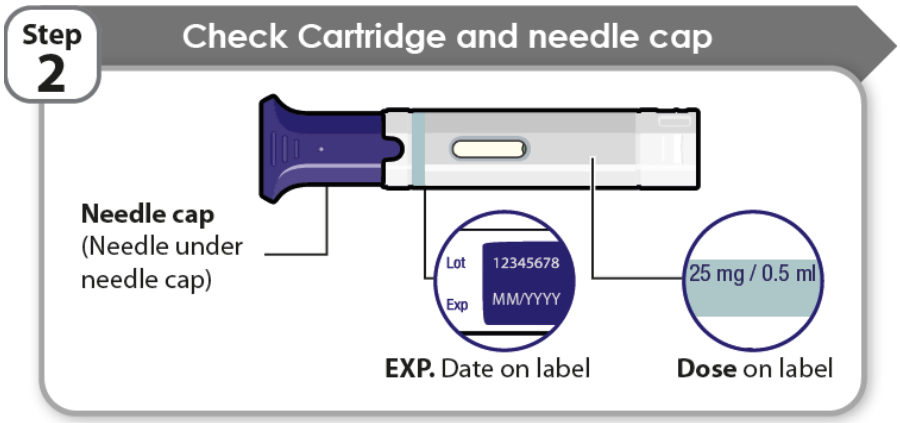
Your Cartridge:



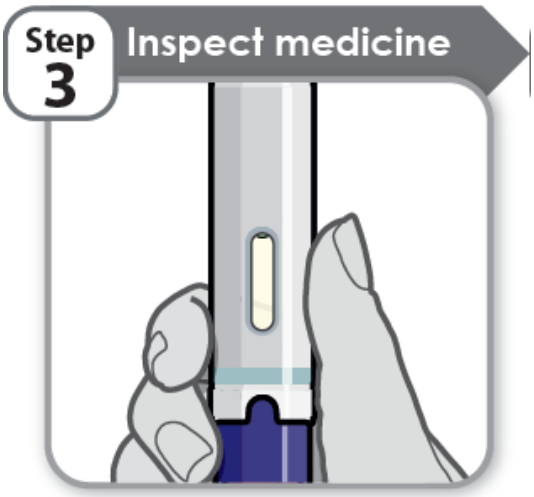
Preparation Steps



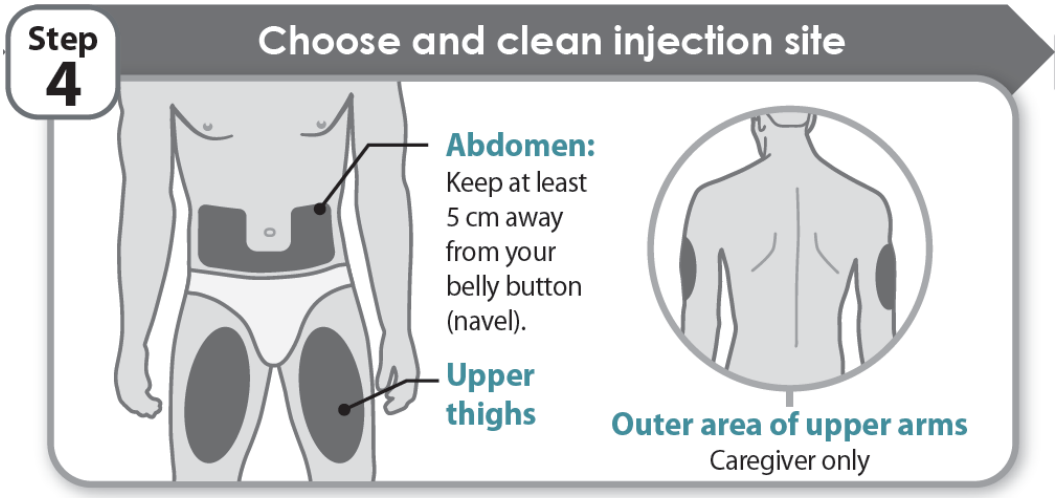
- **Remove** 1 Cartridge from the tray inside the Carton.
- **Put** the Carton and tray with any unused Cartridges back in the refrigerator.
- **Wash** and dry your hands.
- For a more comfortable injection leave your Cartridge at room temperature for approximately **15 - 30 minutes** away from direct sunlight.
  Do not use any other methods to warm up your Cartridge.



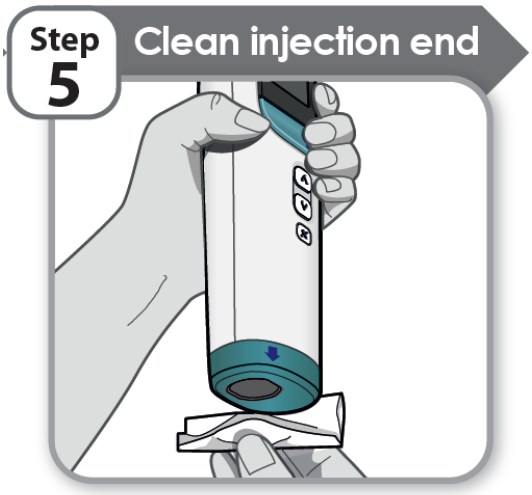
- **Check** the expiry date and medication dose printed on the label. **Do not** use if the expiry date has passed or if it is not your prescribed medication dose.
- **Do not** remove the needle cap until instructed to do so.
- **Check** your Cartridge, **do not** use if:
  - it has been dropped even if it does not look damaged
  - it is damaged
  - the needle cap is loose
  - it has been frozen or exposed to heat
  - it has been at room temperature for more than 4 weeks
  - it has been returned to the refrigerator after reaching room temperature.



- **Inspect** the medicine through the Inspection window, it should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein, this is normal.
- **Do not** use the medicine if it is discoloured, cloudy, or has particles other than those described above.
- **Do not** shake your Cartridge.
  Note: If you have any questions about your medicine, contact your healthcare professional.

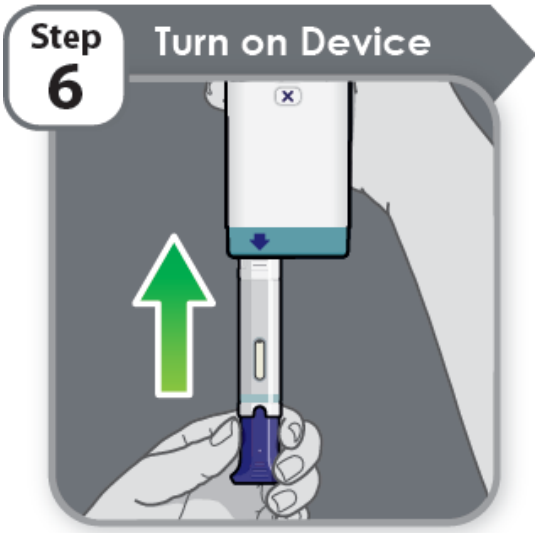


- **Always choose** an area in your abdomen, upper thighs or the outer area of the upper arms (caregiver only).
- **Choose** an injection site at least 3 cm from where you last injected and at least 5 cm away from your belly button (navel).
- **Do not** inject into bony areas or areas on your skin that are broken, bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
- **Do not** inject through your clothes.
  Note: If you have psoriasis, **do not** inject directly into any raised, thick, red, or scaly skin patches or lesions on your skin.
- **Clean** your injection site with the supplied alcohol wipe and **allow to dry**.

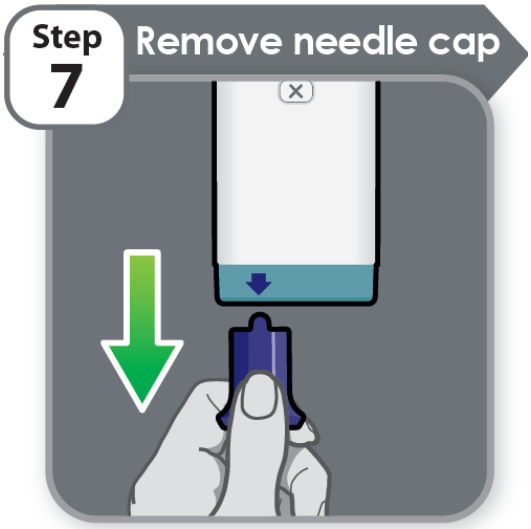


- **Clean** the injection end of your Device with the separate supplied alcohol wipe.
- **Allow** the injection end to dry before giving an injection.

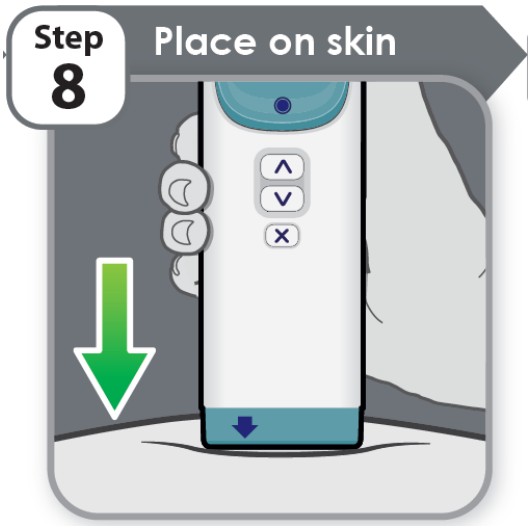
Injection Steps



- **Push** your Cartridge firmly **straight** through the Cartridge door without twisting until you cannot push it any further. Your Device will turn on when your Cartridge has been inserted correctly.
- **Check** the Display shows 25 mg and the expiry date has not passed.
  Note: Your Device will turn off after 90 seconds of inactivity. Press and hold the Injection button to turn your Device back on.



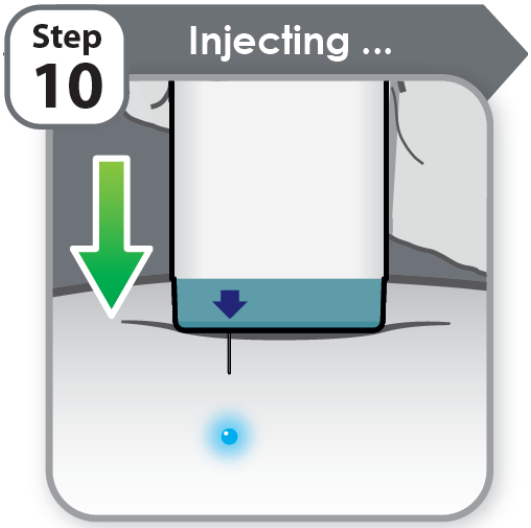
- **Remove** the needle cap by pulling it firmly downwards.
- **Dispose** of the needle cap in a suitable sharps container.
- **Inject** as soon as possible after removing the needle cap.
- **Do not** replace the needle cap.
  Caution: Do not insert your fingers into your Device after removing the needle cap to avoid a needle stick injury.
  Note: To cancel the injection and eject your Cartridge, press the Cancel / Eject button ⊗ for 1 second.



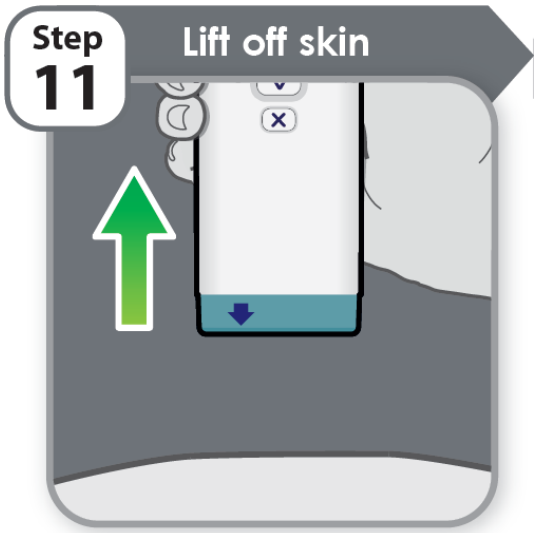
- **Place** your Device with the **blue arrow** pointing at 90 degrees towards your injection site.
- **Make sure** you can see the Display on your Device.
- **Do not** pinch the skin around your injection site.
  Caution: If you drop your Device with a Cartridge inserted, eject and dispose of your Cartridge.
  Refer to the Troubleshooting page in the Device User Manual.



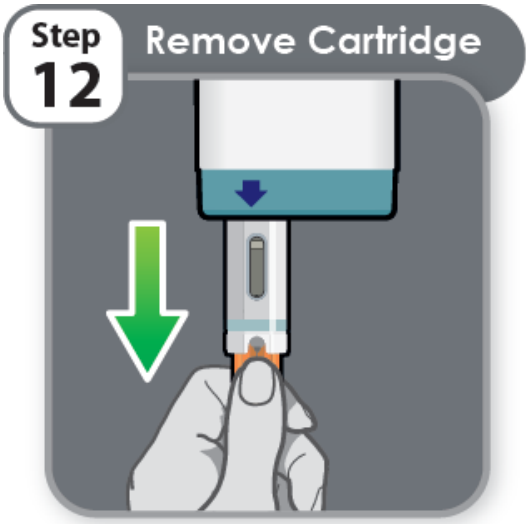
- **Press & hold** the Injection button to begin your injection when instructed by the Display.
  Note: You can release the Injection button after your injection has started.



- **Hold** your Device against your skin and wait while your medication is injected.
- **Watch** the Display on your Device.
- **Do not** move, tilt or remove your Device from your skin until instructed by the Display.
  Note: If you remove your Device before instructed, **do not** place it back on the injection site or inject another dose. Contact your healthcare professional for advice.



- **Lift & hold** your Device away from your skin. Your Device will display that your injection is complete.
- **Wait.** Your Cartridge will be partially ejected from the bottom of your Device. This may take up to 10 seconds.
  Do not cover the bottom of your Device during this time.
  Do not insert your fingers inside your Device as the needle will be exposed during this time.
- If you notice a spot of blood, press a cotton ball or gauze over the injection site until the bleeding stops. **Do not** rub.



- **Pull** your Cartridge straight out after your Device has partially ejected it.
- **Check** your Cartridge is empty of medicine with a grey bar visible in the Inspection window. If not, you may not have received your full dose. Contact your healthcare professional for advice.
- **Do not** reuse your Cartridge or reinsert it into your Device.
- **Dispose** of the used Cartridge straight away in a suitable sharps container as instructed by your healthcare professional or pharmacist and in accordance with local health and safety laws.

--End of Instructions for Use--

Package leaflet: Information for the user

Enbrel 50 mg solution for injection in dose-dispenser cartridge
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Enbrel.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

Information in this leaflet is organised under the following 6 sections:

1. What Enbrel is and what it is used for
2. What you need to know before you use Enbrel
3. How to use Enbrel
4. Possible side effects
5. How to store Enbrel
6. Contents of the pack and other information (See Instructions for use)

1. What Enbrel is and what it is used for

Enbrel is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Enbrel works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Enbrel can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis,** and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For rheumatoid arthritis, Enbrel is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Enbrel can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, Enbrel can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), Enbrel can slow down the structural damage to those joints caused by the disease.

Enbrel is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
    - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years

- Psoriatic arthritis in patients from the age of 12 years

- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them

- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Enbrel

Do not use Enbrel

- if you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if you or the child have, or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child, have an infection of any kind. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Enbrel.

- **Allergic reactions:** If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- **Infections/surgery:** If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Enbrel.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Enbrel.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Enbrel, your doctor will check for signs and symptoms of tuberculosis before starting Enbrel. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Enbrel. Treatment with Enbrel may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Enbrel.
- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Enbrel in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Enbrel.

- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Enbrel is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Enbrel needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Enbrel.
  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
  Children and adults taking Enbrel may have an increased risk of developing lymphoma or another cancer.
  Some children and teenage patients who have received Enbrel or other medicines that work the same way as Enbrel have developed cancers, including unusual types, which sometimes resulted in death.
  Some patients receiving Enbrel have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Enbrel. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Latex:** The needle cover is made from latex (dry natural rubber). Contact your doctor before using Enbrel if the needle cover will be handled by, or Enbrel will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Alcohol abuse:** Enbrel should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- **Wegener's granulomatosis:** Enbrel is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines:** Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Enbrel.

Children and adolescents

Vaccinations: If possible, children should be up to date with all vaccinations before using Enbrel. Some vaccines, such as oral polio vaccine, should not be given while using Enbrel. Please consult the child's doctor before the child receives any vaccines.

Enbrel should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

Other medicines and Enbrel

Tell the doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use Enbrel with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Enbrel should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Enbrel during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Enbrel in pregnancy, compared with mothers who had not received Enbrel or other similar medicines (TNF-antagonists),

but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Enbrel in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Enbrel treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Enbrel during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines

The use of Enbrel is not expected to affect the ability to drive or use machines.

Enbrel contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to use Enbrel

Always use this medicine exactly as the doctor has told you. Check with the doctor or pharmacist if you are not sure.

If you feel that the effect of Enbrel is too strong or too weak, talk to your doctor or pharmacist.

The dose-dispenser cartridge is available in dose strengths of 25 mg and 50 mg.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Enbrel.

Plaque psoriasis

The usual dose is 25 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doctor will decide how long you should take Enbrel and whether retreatment is needed based on your response. If Enbrel has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of Enbrel (10 mg, 25 mg or 50 mg).

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Enbrel per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Enbrel per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of Enbrel per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Enbrel has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

Method and route of administration

Enbrel is administered by an injection under the skin (by subcutaneous injection).

Enbrel can be taken with or without food or drink.

Detailed instructions on how to inject Enbrel are provided in "Instructions for use". Do not mix the Enbrel solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Enbrel should be used.

If you use more Enbrel than you should

If you have used more Enbrel than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Enbrel

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Enbrel

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not inject more Enbrel. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Enbrel, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- **Signs of cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

The known side effects of Enbrel include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people):
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people):
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people):
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to

those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi's sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enbrel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the dose-dispenser cartridge in the outer carton in order to protect from light.

After taking a dose-dispenser cartridge from the refrigerator, wait approximately 15-30 minutes to allow the Enbrel solution in the dose-dispenser cartridge to reach room temperature. Do not warm in any other way. Immediate use is then recommended.

The dose-dispenser cartridges may be stored at room temperature (up to 25°C) for a single period of up to 4 weeks with protection from light; after which they should not be refrigerated again. Enbrel should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that the Enbrel dose-dispenser is removed from the refrigerator and the date after which Enbrel should be discarded (no more than 4 weeks following the removal from the refrigerator).

Inspect the solution in the dose-dispenser cartridge by looking through the inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enbrel contains

Enbrel 50 mg solution for injection in dose-dispenser cartridge
The active substance in Enbrel is etanercept. Each dose-dispenser cartridge contains 1.0 ml of solution, providing 50 mg of etanercept.

The other ingredients are sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate and sodium phosphate dibasic dihydrate, and water for injections.

What Enbrel looks like and contents of the pack

Enbrel is provided as a solution for injection in a ready to use dose-dispenser cartridge. The dose-dispenser cartridge is to be used with SMARTCLIC device. The device is provided separately. The solution is clear to opalescent, colourless to pale yellow or pale brown.

Enbrel 50 mg solution for injection in dose-dispenser cartridge
Cartons contain 2, 4 or 12 dose-dispenser cartridges with 4, 8 or 24 alcohol swabs. Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Instructions for use
Enbrel
(etanercept)
50 mg / 1 ml
For Subcutaneous Injection Only

Important Information

- Keep this Instructions for use, it shows step-by-step how to prepare and give an injection.
- Only use Enbrel after you read and understand this Instructions for use.
- Only use Enbrel after you have received training from your healthcare professional.
- Your Dose Dispenser Cartridge contains a single dose of Enbrel and must only be used with your SMARTCLIC Device.
- Dose Dispenser Cartridge and SMARTCLIC Device will be referred to as "Cartridge" and "Device" in this Instructions for use.
- If this is the first time you are using your Device, make sure you follow the setup instructions in the separate User Manual. You will not be able to use your Device until you complete the setup.
- **Do not** attempt to use your Cartridges with any other Device.
- **Do not** share your Cartridges or your Device with another person.
- **Do not** shake your Cartridges or your Device containing a Cartridge.
- **Do not** remove your Cartridge needle cap until instructed to do so.
- **Do not** reuse your Cartridge if the needle cap has been removed.
- Avoid spilling liquid on your Cartridges or your Device. Never rinse or put your Cartridges or your Device under water.
- Refer to the additional Device User Manual for accessing menus, using a Training Cartridge, advanced use and troubleshooting error messages.

Storage

- Store Cartridges in the refrigerator between 2 ºC to 8 ºC. **Do not** freeze your Cartridges. **Do not** store your Cartridges in your Device.
- Store Cartridges in their original Carton until use to protect from direct sunlight.
- You may store your Cartridges at room temperature up to 25 ºC for up to 4 weeks. **Do not** return them to the refrigerator after they have reached room temperature.
- Keep your Cartridges and your Device out of sight and reach of children and adolescents.
- Refer to your Device User Manual for how to store and clean your Device.

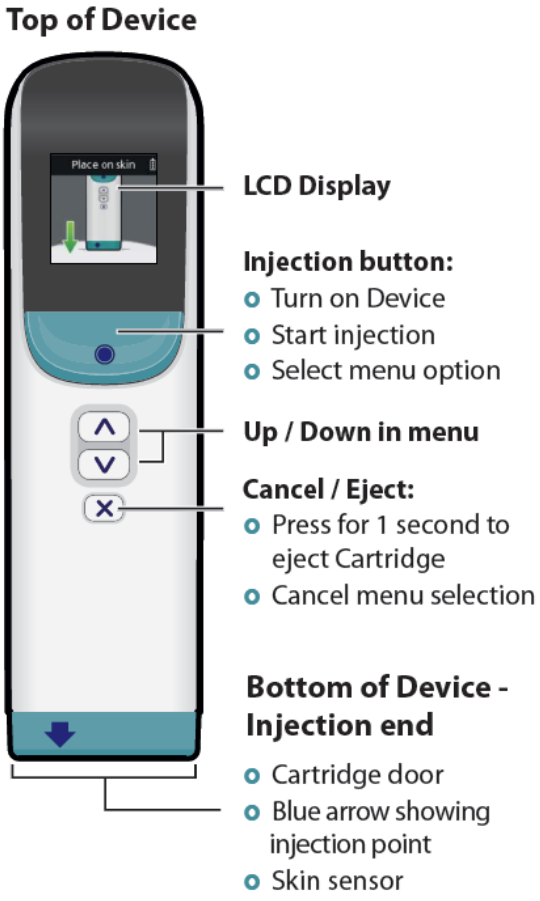
Supplies you need

- **Gather** the following supplies on a clean flat surface:
    - Enbrel Carton containing Cartridges
    - your SMARTCLIC Device
    - alcohol wipes
    - clean cotton balls or gauze pads (not included)
    - a suitable sharps container (not included).

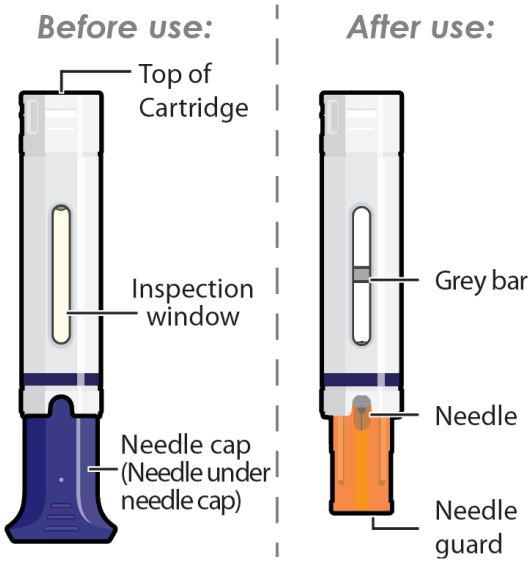
- **Do not** use if the Carton is dropped or damaged.
  Note: If you do not have everything you need, ask your healthcare professional.

Your Device:

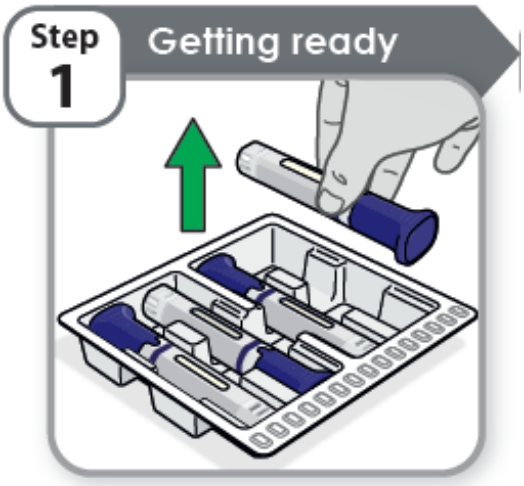
Refer to User Manual for more information.



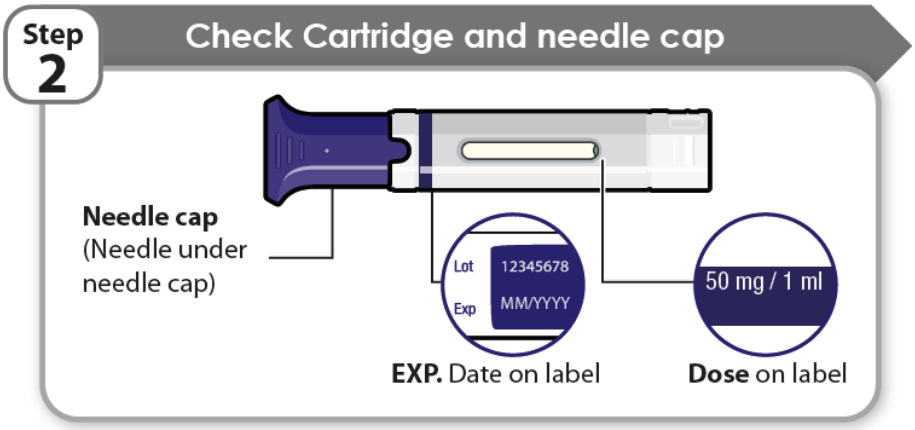
Your Cartridge:



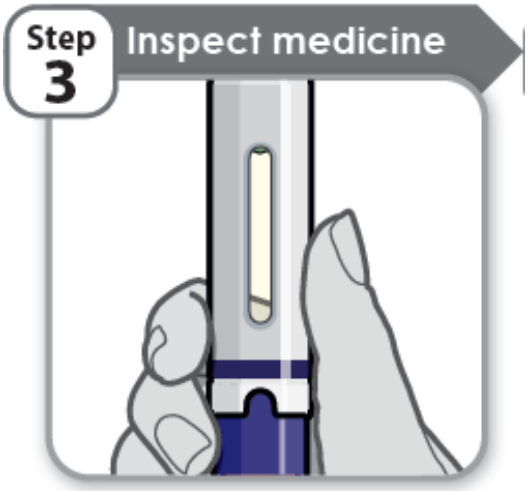
Preparation Steps



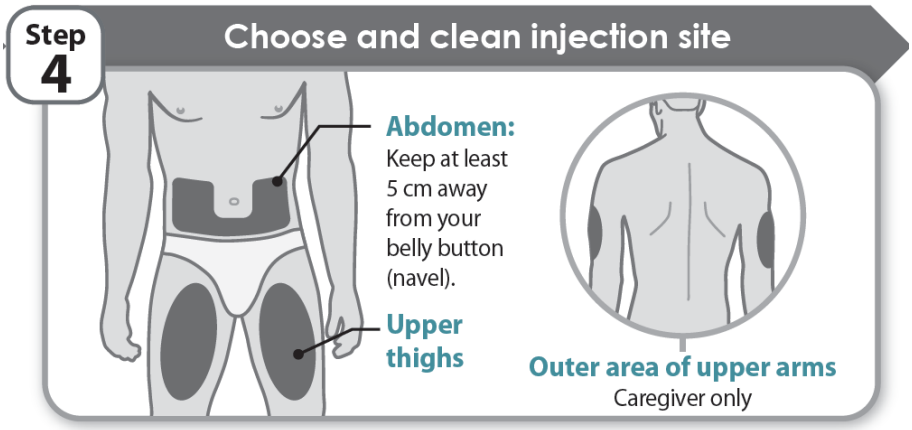
- **Remove** 1 Cartridge from the tray inside the Carton.
- **Put** the Carton and tray with any unused Cartridges back in the refrigerator.
- **Wash** and dry your hands.
- For a more comfortable injection leave your Cartridge at room temperature for approximately **15 - 30 minutes** away from direct sunlight.
  Do not use any other methods to warm up your Cartridge.



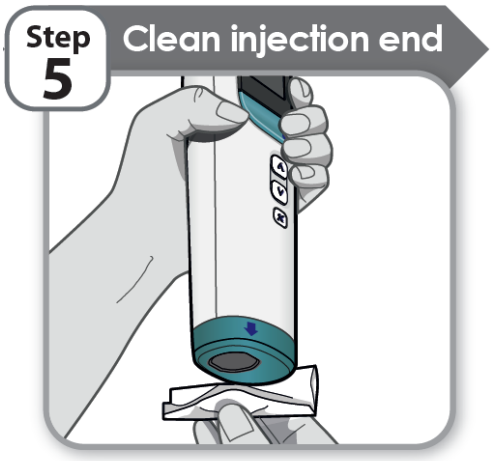
- **Check** the expiry date and medication dose printed on the label. **Do not** use if the expiry date has passed or if it is not your prescribed medication dose.
- **Do not** remove the needle cap until instructed to do so.
- **Check** your Cartridge, **do not** use if:
  - it has been dropped even if it does not look damaged
  - it is damaged
  - the needle cap is loose
  - it has been frozen or exposed to heat
  - it has been at room temperature for more than 4 weeks
  - it has been returned to the refrigerator after reaching room temperature.



- **Inspect** the medicine through the Inspection window, it should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein, this is normal.
- **Do not** use the medicine if it is discoloured, cloudy, or has particles other than those described above.
- **Do not** shake your Cartridge.
  Note: If you have any questions about your medicine, contact your healthcare professional.



- **Always choose** an area in your abdomen, upper thighs or the outer area of the upper arms (caregiver only).
- **Choose** an injection site at least 3 cm from where you last injected and at least 5 cm away from your belly button (navel).
- **Do not** inject into bony areas or areas on your skin that are broken, bruised, red, sore (tender) or hard. Avoid injecting into areas with scars or stretch marks.
- **Do not** inject through your clothes.
  Note: If you have psoriasis, **do not** inject directly into any raised, thick, red, or scaly skin patches or lesions on your skin.
- **Clean** your injection site with the supplied alcohol wipe and **allow to dry**.

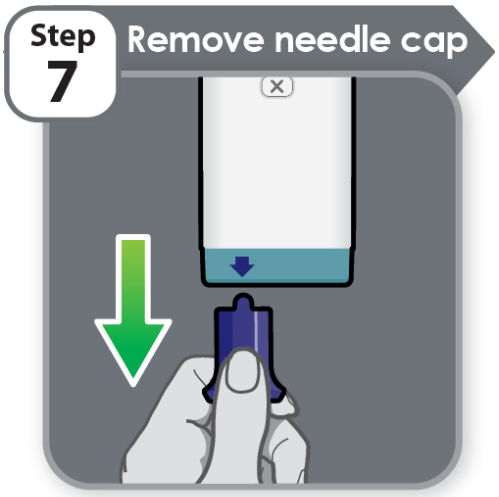


- **Clean** the injection end of your Device with the separate supplied alcohol wipe.
- **Allow** the injection end to dry before giving an injection.

Injection Steps



- **Push** your Cartridge firmly **straight** through the Cartridge door without twisting until you cannot push it any further. Your Device will turn on when your Cartridge has been inserted correctly.
- **Check** the Display shows 50 mg and the expiry date has not passed.
  Note: Your Device will turn off after 90 seconds of inactivity. Press and hold the Injection button to turn your Device back on.



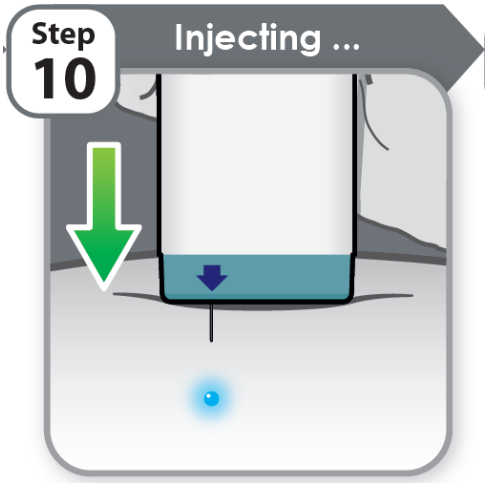
- **Remove** the needle cap by pulling it firmly downwards.
- **Dispose** of the needle cap in a suitable sharps container.
- **Inject** as soon as possible after removing the needle cap.
- **Do not** replace the needle cap.
  Caution: Do not insert your fingers into your Device after removing the needle cap to avoid a needle stick injury.
  Note: To cancel the injection and eject your Cartridge, press the Cancel / Eject button ⊗ for 1 second.



- **Place** your Device with the **blue arrow** pointing at 90 degrees towards your injection site.
- **Make sure** you can see the Display on your Device.
- **Do not** pinch the skin around your injection site.
  Caution: If you drop your Device with a Cartridge inserted, eject and dispose of your Cartridge.
  Refer to the Troubleshooting page in the Device User Manual.



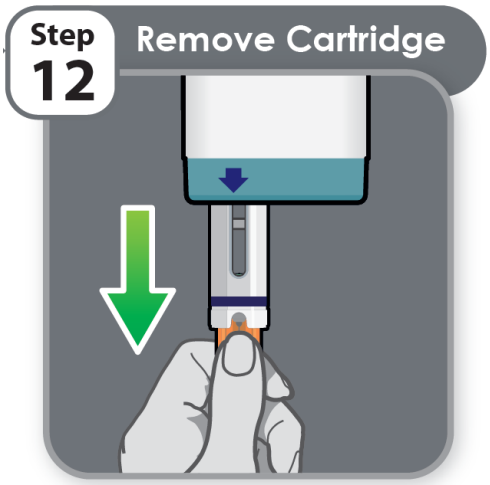
- **Press & hold** the Injection button to begin your injection when instructed by the Display.
  Note: You can release the Injection button after your injection has started.



- **Hold** your Device against your skin and wait while your medication is injected.
- **Watch** the Display on your Device.
- **Do not** move, tilt or remove your Device from your skin until instructed by the Display.
  Note: If you remove your Device before instructed, **do not** place it back on the injection site or inject another dose. Contact your healthcare professional for advice.



- **Lift & hold** your Device away from your skin. Your Device will display that your injection is complete.
- **Wait.** Your Cartridge will be partially ejected from the bottom of your Device. This may take up to 10 seconds.
  Do not cover the bottom of your Device during this time.
  Do not insert your fingers inside your Device as the needle will be exposed during this time.
- If you notice a spot of blood, press a cotton ball or gauze over the injection site until the bleeding stops. **Do not** rub.



- **Pull** your Cartridge straight out after your Device has partially ejected it.
- **Check** your Cartridge is empty of medicine with a grey bar visible in the Inspection window. If not, you may not have received your full dose. Contact your healthcare professional for advice.
- **Do not** reuse your Cartridge or reinsert it into your Device.
- **Dispose** of the used Cartridge straight away in a suitable sharps container as instructed by your healthcare professional or pharmacist and in accordance with local health and safety laws.

--End of Instructions for Use