ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Simponi 45 mg/0.45 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled pen contains 45 mg golimumab* in 0.45 mL. 1 mL solution contains 100 mg golimumab.

Each pre-filled pen can deliver 0.1 mL to 0.45 mL (corresponding to 10 mg to 45 mg golimumab) in increments of 0.05 mL.

* Human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology.

Excipients with known effect
Each pre-filled pen contains 18.5 mg sorbitol (E420) per 45 mg dose.

Each pre-filled pen contains 0.068 mg of polysorbate 80 (E433) per 45 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled pen (VarioJect)

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Juvenile idiopathic arthritis
Polyarticular juvenile idiopathic arthritis (pJIA)
Simponi in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older who have responded inadequately to previous therapy with MTX.

Ulcerative colitis
Paediatric ulcerative colitis (pUC)
Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients 2 years of age and older with a body weight of at least 15 kg, who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

4.2 Posology and method of administration

Treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Simponi is indicated. Patients treated with Simponi should be given the Patient Card which is included in the pack.

Posology
The 45 mg/0.45 mL pre-filled pen is for paediatric patients. Each pre-filled pen is for single use in a single patient, and should be discarded immediately after use.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis in children with body weight less than 40 kg

The recommended dose of Simponi for children with a body weight less than 40 kg with polyarticular juvenile idiopathic arthritis is 30 mg/m^2 body surface area up to maximum single dose of 40 mg administered once a month, on the same date each month. The prescribed volume of injection should be selected according to patient's height and weight as shown in Table 1.

Table 1
Simponi dose in millilitres (mL) by height and weight of patients with pJIA

		Total Body Weight (kg)						
		10-12	**13-17**	**18-22**	**23-27**	**28-32**	**33-37**	**38-39**
		Dose (mL)						
Height (cm)	**70 to < 75**	0.15	0.15	0.2				
	75 to < 85	0.15	0.15	0.2	0.2			
	85 to < 95	0.15	0.2	0.2	0.25	0.25	0.3	
	95 to < 105	0.15	0.2	0.2	0.25	0.25	0.3	0.3
	105 to < 115	0.15	0.2	0.25	0.25	0.3	0.3	0.3
	115 to < 125	0.2	0.2	0.25	0.25	0.3	0.3	0.35
	125 to < 135		0.2	0.25	0.3	0.3	0.35	0.35
	135 to < 145		0.25	0.25	0.3	0.3	0.35	0.35
	145 to < 155			0.25	0.3	0.35	0.35	0.4
	155 to < 165			0.3	0.3	0.35	0.35	0.4
	165 to < 175				0.35	0.35	0.4	0.4
	175 to < 180					0.35	0.4	0.4

Polyarticular juvenile idiopathic arthritis in children with a body weight of at least 40 kg

For children with body weight of at least 40 kg, a 50 mg pre-filled pen or pre-filled syringe is available. For the posology of the 50 mg dosing regimen, see section 4.2 of the Simponi 50 mg pre-filled pen or pre-filled syringe SmPC.

Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in children who show no evidence of therapeutic benefit within this time period.

Ulcerative colitis

Paediatric ulcerative colitis (pUC) in children 2 years of age and older with a body weight of at least 15 kg

The recommended dose of Simponi for patients from 2 to 17 years of age with ulcerative colitis is based on body weight.

For patients with body weight of at least 15 kg to less than 40 kg who are in remission at or after week 54, the physician may consider decreasing the maintenance dose to 25 mg every 4 weeks. To administer this dose, the 45 mg pre-filled pen is available. The prescribed volume of injection to meet this dose is 0.25 mL

For induction and maintenance treatment a 50 mg pre-filled syringe or 100 mg pre-filled syringe is available. For the posology of the 50 mg or 100 mg dosing regimen, see section 4.2 of the Simponi 50 mg or 100 mg pre-filled syringe SmPC.

Missed dose

If a patient forgets to inject Simponi on the planned date, the forgotten dose should be injected as soon as the patient remembers. Patients should be instructed not to inject a double dose to make up for the forgotten dose.

The next dose should be administered based on the following guidance:

- if the dose is less than 2 weeks late, the patient should inject the forgotten dose and stay on the original schedule.
- if the dose is more than 2 weeks late, the patient should inject the forgotten dose and a new schedule should be established from the date of this injection.

Special populations
Renal and hepatic impairment
Simponi has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
There is no relevant use of Simponi in children aged less than 2 years in pJIA or pUC.

Method of administration
Simponi is for subcutaneous use. After proper training in subcutaneous injection technique, patients may self-inject if their physician determines that this is appropriate, with medical follow-up as necessary. Patients should be instructed to inject the prescribed amount of Simponi according to the comprehensive instructions for use provided in the pack. Each pre-filled pen is for single use in a single patient, and should be discarded immediately after use.

For administration instructions, see section 6.6.

4.3 Contraindications

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

Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate or severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Patients must be monitored closely for infections including tuberculosis before, during and after treatment with golimumab. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. Further treatment with golimumab must not be given if a patient develops a serious infection or sepsis (see section 4.3).

Golimumab should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of golimumab in patients with a chronic infection or a history of recurrent infection. Patients should be advised of, and avoid exposure to, potential risk factors for infection as appropriate.

Patients taking TNF-blockers are more susceptible to serious infections.
Bacterial (including sepsis and pneumonia), mycobacterial (including TB), invasive fungal and opportunistic infections, including fatalities, have been reported in patients receiving golimumab. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with golimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of golimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of golimumab treatment should be carefully considered before initiation of golimumab therapy. In at-risk patients treated with golimumab, an invasive fungal infection should be suspected if they develop a serious systemic illness. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections, if feasible.

Tuberculosis
There have been reports of tuberculosis in patients receiving golimumab. It should be noted that in the majority of these reports, tuberculosis was extrapulmonary presenting as either local or disseminated disease.

Before starting treatment with golimumab, 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 or blood 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, golimumab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of golimumab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of golimumab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of golimumab. Use of anti-tuberculosis therapy should also be considered before the initiation of golimumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Cases of active tuberculosis have occurred in patients treated with golimumab during and after treatment for latent tuberculosis. Patients receiving golimumab should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

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 golimumab treatment.

Hepatitis B virus reactivation
Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including golimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with golimumab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with golimumab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, golimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Malignancies and lymphoproliferative disorders
The potential role of TNF-blocking therapy in the development of malignancies is not known. Based on the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

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

Lymphoma and leukaemia
In the controlled portions of clinical trials of all the TNF-blocking agents including golimumab, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the Simponi Phase IIb and Phase III clinical trials in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), the incidence of lymphoma in golimumab-treated patients was higher than expected in the general population. Cases of leukaemia have been reported in patients treated with golimumab. 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.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with other TNF-blocking agents (see section 4.8). This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of cases have occurred in adolescent and young adult males with nearly all on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) for inflammatory bowel disease. The potential risk with the combination of AZA or 6-MP and golimumab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Malignancies other than lymphoma
In the controlled portions of the Simponi Phase IIb and Phase III clinical trials in RA, PsA, AS, and ulcerative colitis (UC), the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups.

Colon dysplasia/carcinoma
It is not known if golimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with golimumab, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

In an exploratory clinical trial evaluating the use of golimumab in patients with severe persistent asthma, more malignancies were reported in patients treated with golimumab compared with control patients (see section 4.8). The significance of this finding is unknown.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with an increased risk of malignancy due to heavy smoking.

Skin cancers
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents, including golimumab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

Congestive heart failure (CHF)
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including golimumab. Some cases had a fatal outcome. In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to CHF have been observed. Golimumab has not been studied in patients with CHF. Golimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and golimumab must be discontinued in patients who develop new or worsening symptoms of heart failure (see section 4.3).

Neurological events
Use of TNF-blocking agents, including golimumab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy. Discontinuation of golimumab should be considered if these disorders develop (see section 4.8).

Surgery
There is limited safety experience of golimumab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on golimumab should be closely monitored for infections, and appropriate actions should be taken.

Immunosuppression
The possibility exists for TNF-blocking agents, including golimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Autoimmune processes
The relative deficiency of TNF_{α} caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with golimumab and is positive for antibodies against double-stranded DNA, treatment with golimumab should be discontinued (see section 4.8).

Haematologic reactions
There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anaemia, and thrombocytopenia in patients receiving TNF-blockers, including golimumab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of golimumab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent administration of TNF-antagonists and anakinra
Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. The combination of golimumab and anakinra is not recommended.

Concurrent administration of TNF-antagonists and abatacept
In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of golimumab and abatacept is not recommended.

Concurrent administration with other biological therapeutics
There is insufficient information regarding the concomitant use of golimumab with other biological therapeutics used to treat the same conditions as golimumab. The concomitant use of golimumab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological disease modifying anti-rheumatic drugs (DMARDs)
Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Vaccinations/therapeutic infectious agents
Patients treated with golimumab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6). In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g. BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with golimumab.

Allergic reactions
In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following golimumab administration. Some of these reactions occurred after the first administration of golimumab. If an anaphylactic reaction or other serious allergic reactions occur, administration of golimumab should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity
The needle cover on the pre-filled pen is manufactured from dry natural rubber containing latex, and may cause allergic reactions in individuals sensitive to latex.

Special populations

Elderly (≥ 65 years)
In the Phase III studies in RA, PsA, AS, and UC, no overall differences in adverse events (AEs), serious adverse events (SAEs), and serious infections in patients age 65 or older who received golimumab 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. There were no patients age 45 and over in the non-radiographic axial spondyloarthritis (nr-Axial SpA) study.

Renal and hepatic impairment
Specific studies of golimumab have not been conducted in patients with renal or hepatic impairment. Golimumab should be used with caution in subjects with impaired hepatic function (see section 4.2).

Paediatrics
Vaccinations
If possible, it is recommended that prior to initiating golimumab therapy, paediatric patients be brought up to date with all immunisations in agreement with current immunisation guidelines (see Vaccinations/ therapeutic infectious agents above).

Excipients with known effect
Sorbitol
Simponi contains sorbitol (E420). In patients with rare hereditary problems of fructose intolerance, the additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account (see section 2).

Polysorbate 80
Simponi contains 0.068 mg of polysorbate 80 (E433) in each pre-filled pen. Polysorbates may cause allergic reactions (see section 2).

Potential for medication errors
It is important that the correct dose is administered as indicated in the posology (see section 4.2). Care should be taken to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with other biological therapeutics
The combination of golimumab with other biological therapeutics used to treat the same conditions as golimumab, including anakinra and abatacept is not recommended (see section 4.4).

Live vaccines/therapeutic infectious agents
Live vaccines should not be given concurrently with golimumab (see sections 4.4 and 4.6).

Therapeutic infectious agents should not be given concurrently with golimumab (see section 4.4).

Methotrexate
Although concomitant use of MTX results in higher steady-state trough concentrations of golimumab in patients with RA, PsA or AS, the data do not suggest the need for dose adjustment of either golimumab or MTX (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last golimumab treatment.

Pregnancy
There is a moderate amount (approximately 400) of prospectively collected pregnancies exposed to golimumab resulting in live birth with known outcomes, including 220 pregnancies exposed during the first trimester. In a population-based study from Northern Europe including 131 pregnancies (and 134 infants), there were 6/134 (4.5%) events of major congenital anomalies following *in utero* exposure to Simponi vs 599/10,823 (5.5%) events for non-biologic systemic therapy compared to 4.6% in the general population of the study. Confounder-adjusted odds ratios were OR 0.79 (95% CI 0.35-1.81) for Simponi vs. non-biologic systemic therapy and OR 0.95 (95% CI 0.42-2.16) for Simponi vs. the general population, respectively.

Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with

respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The available clinical experience is limited. Golimumab should only be used during pregnancy if clearly needed.

Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see sections 4.4 and 4.5).

Breast-feeding
It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Golimumab was shown to pass over to breast milk in monkeys, and because human immunoglobulins are excreted in milk, women must not breast feed during and for at least 6 months after golimumab treatment.

Fertility
No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, showed no relevant effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Simponi has minor influence on the ability to ride bicycles, drive and use machines. Dizziness may however occur following administration of Simponi (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
In the controlled period of the pivotal trials in RA, PsA, AS, nr-Axial SpA, and UC, upper respiratory tract infection was the most common adverse reaction (AR) reported in 12.6% of golimumab-treated patients compared with 11.0% of control patients. The most serious ARs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome), haematologic reactions, serious systemic hypersensitivity (including anaphylactic reaction), vasculitis, lymphoma and leukaemia (see section 4.4).

Tabulated list of adverse reactions
ARs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed in Table 2. Within the designated system organ classes, the ARs are listed under headings of frequency and using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2
Tabulated list of ARs

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)
Common:	Bacterial infections (such as cellulitis), lower respiratory tract infection (such as pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess
Uncommon:	Sepsis including septic shock, pyelonephritis

Rare:	Tuberculosis, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), hepatitis B reactivation, bacterial arthritis, infective bursitis
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia, melanoma, Merkel cell carcinoma
Not known:	Hepatosplenic T-cell lymphoma*, Kaposi's sarcoma
Blood and lymphatic system disorders	
Common:	Leukopenia (including neutropenia), anaemia
Uncommon:	Thrombocytopenia, pancytopenia
Rare:	Aplastic anaemia, agranulocytosis
Immune system disorders	
Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis
Endocrine disorders	
Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders	
Uncommon:	Blood glucose increased, lipids increased
Psychiatric disorders	
Common:	Depression, insomnia
Nervous system disorders	
Common:	Dizziness, headache, paraesthesia
Uncommon:	Balance disorders
Rare:	Demyelinating disorders (central and peripheral), dysgeusia
Eye disorders	
Uncommon:	Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritus and irritation)
Cardiac disorders	
Uncommon:	Arrhythmia, ischaemic coronary artery disorders
Rare:	Congestive heart failure (new onset or worsening)
Vascular disorders	
Common:	Hypertension
Uncommon:	Thrombosis (such as deep venous and aortic), flushing
Rare:	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	Asthma and related symptoms (such as wheezing and bronchial hyperactivity)
Uncommon:	Interstitial lung disease
Gastrointestinal disorders	
Common:	Dyspepsia, gastrointestinal and abdominal pain, nausea, gastrointestinal inflammatory disorders (such as gastritis and colitis), stomatitis
Uncommon:	Constipation, gastro-oesophageal reflux disease
Hepatobiliary disorders	
Common:	Alanine aminotransferase increased, aspartate aminotransferase increased
Uncommon:	Cholelithiasis, hepatic disorders

Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia, dermatitis
Uncommon:	Bullous skin reactions, psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria
Rare:	Lichenoid reactions, skin exfoliation, vasculitis (cutaneous)
Not known:	Worsening of symptoms of dermatomyositis
Musculoskeletal and connective tissue disorders	
Rare:	Lupus-like syndrome
Renal and urinary disorders	
Rare:	Bladder disorders, renal disorders
Reproductive system and breast disorders	
Uncommon:	Breast disorders, menstrual disorders
General disorders and administration site conditions	
Common:	Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia), chest discomfort
Rare:	Impaired healing
Injury, poisoning and procedural complications	
Common:	Bone fractures

* Observed with other TNF-blocking agents.

Throughout this section, median duration of follow-up (approximately 4 years) is generally presented for all golimumab use. Where golimumab use is described by dose, the median duration of follow-up varies (approximately 2 years for 50 mg dose, approximately 3 years for 100 mg dose) as patients may have switched between doses.

Description of selected adverse reactions

Infections
In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of golimumab-treated patients (incidence per 100 subject-years: 60.8; 95% CI: 55.0, 67.1) compared with 11.0% of control patients (incidence per 100 subject-years: 54.5; 95% CI: 46.1, 64.0). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 4 years, the incidence per 100 subject-years of upper respiratory tract infections was 34.9 events; 95% CI: 33.8, 36.0 for golimumab treated patients.

In the controlled period of pivotal trials, infections were observed in 23.0% of golimumab-treated patients (incidence per 100 subject-years: 132.0; 95% CI: 123.3, 141.1) compared with 20.2% of control patients (incidence per 100 subject-years: 122.3; 95% CI: 109.5, 136.2). In controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per 100 subject-years of infections was 81.1 events; 95% CI: 79.5, 82.8 for golimumab treated patients.

In the controlled period of RA, PsA, AS, and nr-Axial SpA trials, serious infections were observed in 1.2% of golimumab-treated patients and 1.2% of control-treated patients. The incidence of serious infections per 100 subject-years of follow-up in the controlled period of RA, PsA, AS, and nr-Axial SpA trials was 7.3; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 2.9; 95% CI: 1.2, 6.0 for the golimumab 50 mg group and 3.6; 95% CI: 1.5, 7.0 for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of golimumab-treated patients compared with 1.5% of control-treated patients. Serious infections observed in golimumab-treated patients included tuberculosis, bacterial infections including sepsis and pneumonia, invasive fungal infections and other opportunistic infections. Some of these infections have been fatal. In the controlled and uncontrolled portions of the pivotal trials with a median follow-up of up to

3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 4.1; 95% CI: 3.6, 4.5, in patients receiving golimumab 100 mg and 2.5; 95% CI: 2.0, 3.1, in patients receiving golimumab 50 mg.

Malignancies
Lymphoma
The incidence of lymphoma in golimumab-treated patients during the pivotal trials was higher than expected in the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Lymphoma was diagnosed in 11 subjects (1 in the golimumab 50 mg treatment groups and 10 in the golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.03 (0.00, 0.15) and 0.13 (0.06, 0.24) events for golimumab 50 mg and 100 mg respectively and 0.00 (0.00, 0.57) events for the placebo. The majority of lymphomas occurred in study GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease (see section 4.4).

Malignancies other than lymphoma
In the controlled periods of pivotal trials and through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar to the general population.

In the controlled and uncontrolled periods of pivotal trials with a median follow-up of up to 3 years, non-melanoma skin cancer was diagnosed in 5 placebo-treated, 10 golimumab 50 mg-treated and 31 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.36 (0.26, 0.49) for combined golimumab and 0.87 (0.28, 2.04) for placebo.

In the controlled and uncontrolled period of pivotal trials with a median follow-up of up to 3 years, malignancies besides melanoma, non-melanoma skin cancer and lymphoma were diagnosed in 5 placebo-treated, 21 golimumab 50 mg-treated and 34 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.48 (0.36, 0.62) for combined golimumab and 0.87 (0.28, 2.04) for placebo (see section 4.4).

Cases reported in clinical studies in asthma
In an exploratory clinical study, patients with severe persistent asthma received a golimumab loading dose (150% of the assigned treatment dose) subcutaneously at week 0 followed by golimumab 200 mg, golimumab 100 mg or golimumab 50 mg every 4 weeks subcutaneously through week 52. Eight malignancies in the combined golimumab treatment group (n = 230) and none in the placebo treatment group (n = 79) were reported. Lymphoma was reported in 1 patient, non-melanoma skin cancer in 2 patients, and other malignancies in 5 patients. There was no specific clustering of any type of malignancy.

During the placebo-controlled portion of the study, the incidence (95% CI) of all malignancies per 100 subject-years of follow-up was 3.19 (1.38, 6.28) in the golimumab group. In this study, the incidence (95% CI) per 100 subject-years of follow-up in golimumab-treated subjects was 0.40 (0.01, 2.20) for lymphoma, 0.79 (0.10, 2.86) for non-melanoma skin cancers, and 1.99 (0.64, 4.63) for other malignancies. For placebo subjects, the incidence (95% CI) per 100 subject-years of follow-up of these malignancies was 0.00 (0.00, 2.94). The significance of this finding is unknown.

Neurological events
In the controlled and uncontrolled periods of the pivotal trials with a median follow-up of up to 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg (see section 4.4).

Liver enzyme elevations
In the controlled period of RA and PsA pivotal trials, mild ALT elevations (> 1 and < 3 x upper limit of normal (ULN)) occurred in similar proportions of golimumab and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS and nr-Axial SpA studies, more golimumab-treated patients (26.9%) than control patients (10.6%) had mild ALT elevations. In the controlled and uncontrolled periods of the RA and PsA pivotal trials, with a median follow-up of approximately 5 years, the incidence of mild ALT elevations was similar in golimumab-treated and control patients in RA and PsA studies. In the controlled period of the UC pivotal trials of golimumab induction, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of golimumab-treated and control patients (8.0% to 6.9%, respectively). In controlled and uncontrolled periods of the UC pivotal trials with a median follow-up of approximately 2 years, the proportion of patients with mild ALT elevations was 24.7% in patients receiving golimumab during the maintenance portion of the UC study.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5 x ULN were uncommon and seen in more golimumab-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. In the controlled and uncontrolled periods of RA, PsA and AS pivotal trials, with a median follow-up of 5 years, the incidence of ALT elevations ≥ 5 x ULN was similar in both golimumab-treated and control patients. In general these elevations were asymptomatic and the abnormalities decreased or resolved with either continuation or discontinuation of golimumab or modification of concomitant medicinal products. No cases were reported in the controlled and uncontrolled periods of the nr-Axial SpA study (up to 1 year). In the controlled periods of the pivotal UC trials, of golimumab induction, ALT elevations ≥ 5 x ULN occurred in similar proportions of golimumab-treated patients compared to placebo-treated patients (0.3% to 1.0%, respectively). In the controlled and uncontrolled periods of the pivotal UC trials with a median follow-up of approximately 2 years, the proportion of patients with ALT elevations ≥ 5 x ULN was 0.8% in patients receiving golimumab during the maintenance portion of the UC study.

Within the RA, PsA, AS, and nr-Axial SpA pivotal trials, one patient in an RA trial with pre-existing liver abnormalities and confounding medicinal products treated with golimumab developed non-infectious fatal hepatitis with jaundice. The role of golimumab as a contributing or aggravation factor cannot be excluded.

Injection site reactions
In the controlled periods of pivotal trials, 5.4% of golimumab-treated patients had injection site reactions compared with 2.0% in control patients. The presence of antibodies to golimumab may increase the risk of injection site reactions. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

In controlled Phase IIb and/or III trials in RA, PsA, AS, nr-Axial SpA, severe persistent asthma, and Phase II/III trials in UC, no patients treated with golimumab developed anaphylactic reactions.

Autoimmune antibodies
In the controlled and uncontrolled periods of pivotal trials through 1 year of follow-up, 3.5% of golimumab-treated patients and 2.3% of control patients were newly ANA-positive (at titres of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients anti-dsDNA negative at baseline was 1.1%.

Paediatric population
Polyarticular juvenile idiopathic arthritis
The safety of golimumab has been studied in a Phase III study of 173 pJIA patients from 2 to 17 years of age. The average follow-up was approximately two years. In this study, the type and frequency of adverse events reported were generally similar to those seen in adult RA studies.

Ulcerative colitis
The safety of golimumab has been studied in a Phase III study of 69 patients from 4 to 17 years of age with moderately to severely active ulcerative colitis. In this study, adverse reactions observed were consistent with the established safety profile of golimumab in adult patients with UC.

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

Single doses up to 10 mg/kg intravenously have been administered in a clinical study without dose-limiting toxicity. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors, ATC code: L04AB06

Mechanism of action
Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors.

Pharmacodynamic effects
The binding of human TNF by golimumab was shown to neutralise TNF-α-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. *In vitro*, TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab.

Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with Simponi resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix-metalloproteinase (MMP)-3 and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNF-α were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients. These changes were observed at the first assessment (week 4) after the initial Simponi administration and were generally maintained through week 24.

Clinical efficacy

Polyarticular juvenile idiopathic arthritis
The safety and efficacy of Simponi was evaluated in a randomised, double-blind, placebo-controlled, withdrawal study (GO-KIDS) in 173 children (2 to 17 years of age) with active pJIA with at least 5 active joints and an inadequate response to MTX. Children with polyarticular course JIA (rheumatoid factor positive or negative polyarthritis, extended oligoarthritis, juvenile psoriatic arthritis or systemic JIA with no current systemic symptoms) were included in the study. The baseline median number of active joints was 12, and median CRP was 0.17 mg/dL.

Part 1 of the study consisted of a 16-week open-label phase in which 173 enrolled children received Simponi 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks and MTX. The 154 children who

achieved an American College of Rheumatology (ACR) Ped 30 response at week 16 entered Part 2 of the study, the randomised withdrawal phase, and received Simponi 30 mg/m^2 (maximum 50 mg) + MTX or placebo + MTX every 4 weeks. After disease flare, children received Simponi 30 mg/m^2 (maximum 50 mg) + MTX. At week 48, children entered a long-term extension.

Children in this study demonstrated ACR Ped 30, 50, 70, and 90 responses from week 4.

At week 16, 87% of children were ACR Ped 30 responders, and 79%, 66%, and 36% of children were ACR Ped 50, ACR Ped 70, and ACR Ped 90 responders, respectively. At week 16, 34% of children had inactive disease defined as having the presence of all of the following: no joints with active arthritis; no fever, rash, serositis, splenomegaly, hepatomegaly, or generalised lymphadenopathy attributable to JIA; no active uveitis; normal ESR (< 20 mm/hour) or CRP (< 1.0 mg/dL); physician global assessment of disease activity (≤ 5 mm on the VAS); duration of morning stiffness < 15 minutes.

At week 16, all ACR Ped components demonstrated clinically relevant improvement from baseline (see Table 3).

Table 3
Improvements from baseline in ACR Ped components at week 16[a]

	Median percent improvement
	Simponi 30 mg/m^2 n[b] = 173
Physicians global assessment of disease (VAS[c] 0-10 cm)	88%
Subject/parent global assessment of overall well-being (VAS 0-10 cm)	67%
Number of active joints	92%
Number of joints with limited range of motion	80%
Physical function by CHAQ[d]	50%
ESR (mm/h)[e]	33%

[a] baseline = week 0
[b] "n" reflects enrolled patients
[c] VAS: Visual Analogue Scale
[d] CHAQ: Child Health Assessment Questionnaire
[e] ESR (mm/h): erythrocyte sedimentation rate (millimetres per hour)

The primary endpoint, the proportion of children who were ACR Ped 30 responders at week 16 and who did not experience a flare between week 16 and week 48, was not achieved. The majority of children did not experience a flare between week 16 and week 48 (59% in the Simponi + MTX and 53% in the placebo + MTX groups, respectively; p = 0.41).

Pre-specified subgroup analyses of the primary endpoint by baseline CRP (≥ 1 mg/dL vs < 1 mg/dL) demonstrated higher flare rates in placebo + MTX vs Simponi + MTX treated subjects among subjects with baseline CRP ≥ 1 mg/dL (87% vs 40% p = 0.0068).

At week 48, 53% and 55% of children in the Simponi + MTX group and placebo + MTX group, respectively, were ACR Ped 30 responders, and 40% and 28% of children in the Simponi + MTX group and placebo + MTX group, respectively, achieved inactive disease.

Adult rheumatoid arthritis
The efficacy of Simponi was demonstrated in three multi-centre, randomised, double-blind, placebo-controlled studies in over 1500 patients ≥ 18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening. Patients had at least 4 swollen and 4 tender joints. Simponi or placebo were subcutaneously administered every 4 weeks.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. Patients receiving placebo + MTX were switched to Simponi 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

GO-AFTER evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomised to receive placebo, Simponi 50 mg, or Simponi 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Simponi 50 mg + MTX.

In GO-FORWARD, the (co-) primary endpoints were the percentage of patients achieving an ACR 20 response at week 14 and the improvement from baseline in Health Assessment Questionnaire (HAQ) at week 24. In GO-AFTER, the primary endpoint was the percentage of patients achieving an ACR 20 response at week 14. In GO-BEFORE, the co-primary endpoints were the percentage of patients achieving ACR 50 response at week 24 and the change from baseline in the van der Heijde-modified Sharp (vdH-S) score at week 52. In addition to the primary endpoint(s), additional assessments of the impact of Simponi treatment on the signs and symptoms of arthritis, radiographic response, physical function and health-related quality of life were performed.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens with concomitant MTX, through week 104 in GO-FORWARD and GO-BEFORE and through week 24 in GO-AFTER. In each of the RA studies by study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms

Key ACR results for the Simponi 50 mg dose at weeks 14, 24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 4 and are described below. Responses were observed at the first assessment (week 4) after the initial Simponi administration.

In GO-FORWARD, among 89 subjects randomised to Simponi 50 mg + MTX, 48 were still on this treatment at week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving Simponi than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 4
Key efficacy outcomes from the controlled portions of GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	Simponi 50 mg + MTX	Placebo	Simponi 50 mg	Placebo + MTX	Simponi 50 mg + MTX
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA
Week 24	28%	60%*	16%	31% p = 0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p = 0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p = 0.008	2%	10% p = 0.005	NA	NA
Week 24	5%	20%*	2%	9% p = 0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.
* $p \leq 0.001$
NA: Not Applicable

In GO-BEFORE the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Simponi 50 and 100 mg + MTX groups vs MTX alone for ACR50) was not statistically significant at week 24 ($p = 0.053$). At week 52 in the overall population, the percentage of patients in the Simponi 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 4). Additional analyses were performed in subsets representative of the indicated population of patients with severe, active and progressive RA. A generally greater effect of Simponi 50 mg + MTX versus MTX alone was demonstrated in the indicated population compared with the overall population.

In GO-FORWARD and GO-AFTER, clinically meaningful and statistically significant responses in Disease Activity Scale (DAS)28 were observed at each prespecified time point, at week 14 and at week 24 ($p \leq 0.001$). Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 responses were similar from week 104 through week 256.

In GO-BEFORE, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At week 52, 15% of patients in the Simponi 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group ($p = 0.018$). Among 159 subjects randomised to Simponi 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response were observed from week 104 through week 256.

Radiographic response
In GO-BEFORE the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space

narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Simponi 50 mg dose at week 52 are presented in Table 5.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the Simponi treatment group than in the control group (p = 0.003). The radiographic effects observed at week 52 were maintained through week 104. Among patients remaining in the study and treated with Simponi, radiographic effects were similar from week 104 through week 256.

Table 5
Radiographic mean (SD) changes from baseline in total vdH-S score at week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Simponi 50 mg + MTX**
n[a]	**160**	**159**
Total Score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion Score		
Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.7 (2.8)	0.5 (2.1)
JSN Score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)**

[a] n reflects randomised patients
* p = 0.015
** p = 0.044

Physical function and health-related quality of life
Physical function and disability were assessed as a separate endpoint in GO-FORWARD and GO-AFTER using the disability index of the HAQ DI. In these studies, Simponi demonstrated clinically meaningful and statistically significant improvement in HAQ DI from baseline versus control at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement in HAQ DI was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement in HAQ DI was similar from week 104 through week 256.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with Simponi versus placebo at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement of the SF-36 physical component was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement of the SF-36 physical component was similar from week 104 through week 256. In GO-FORWARD and GO-AFTER, statistically significant improvements were observed in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F).

Adult psoriatic arthritis
The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months and had at least mild psoriatic disease. Patients with each sub-type of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). Previous treatment with an anti-TNF agent was not allowed. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg, or

Simponi 100 mg. Patients receiving placebo were switched to Simponi 50 mg after week 24. Patients entered an open label long-term extension at week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at week 14 and change from baseline in total PsA modified vdH-S score at week 24.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 104. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms
Key results for the 50 mg dose at weeks 14 and 24 are shown in Table 6 and described below.

Table 6
Key efficacy outcomes from GO-REVEAL

	Placebo	Simponi 50 mg*
n[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	**9%**	**51%**
Week 24	12%	52%
ACR 50		
Week 14	2%	30%
Week 24	4%	32%
ACR 70		
Week 14	1%	12%
Week 24	1%	19%
PASI[b] 75[c]		
Week 14	3%	40%
Week 24	1%	56%

* $p < 0.05$ for all comparisons;

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

[b] *Psoriasis Area and Severity Index*

[c] Based on the subset of patients with ≥ 3% BSA involvement at baseline, 79 patients (69.9%) in the placebo group and 109 (74.3%) in the Simponi 50 mg group.

Responses were observed at the first assessment (week 4) after the initial Simponi administration. Similar ACR 20 responses at week 14 were observed in patients with polyarticular arthritis with no rheumatoid nodules and asymmetric peripheral arthritis PsA subtypes. The number of patients with other PsA subtypes was too small to allow meaningful assessment. Responses observed in the Simponi treated groups were similar in patients receiving and not receiving concomitant MTX. Among 146 patients randomised to Simponi 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 ($p < 0.05$).

At week 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Simponi-treated patients. Simponi treatment resulted in significant improvement in physical function as assessed by HAQ DI, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36. Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 and HAQ DI

responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 and HAQ DI responses were similar from week 104 through week 256.

Radiographic response
Structural damage in both hands and feet was assessed radiographically by the change from baseline in the vdH-S score, modified for PsA by addition of hand distal interphalangeal (DIP) joints.

Simponi 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean ± SD score was 0.27 ± 1.3 in the placebo group compared with -0.16 ± 1.3 in the Simponi group; p = 0.011). Out of 146 patients who were randomised to Simponi 50 mg, 52 week X-ray data were available for 126 patients, of whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline. Among patients remaining in the study and treated with Simponi, similar rates of patients showed no progression from baseline from week 104 through week 256.

Paediatric ulcerative colitis
The safety and efficacy of Simponi was evaluated in a Phase III multi-centre, open-label, study (PURSUIT 2) designed to enroll children 2 to 17 years of age with moderately to severely active UC defined as a baseline full Mayo score of 6 through 12, inclusive, with an endoscopy subscore of ≥ 2. Children with prior exposure to anti-TNF-α agents were ineligible for participation. The majority of the 69 participants (97.1%) were receiving UC-related medications (corticosteroids, immunomodulators, and/or 5-ASA); 52.2% of participants were receiving corticosteroids, and 88.4% were receiving oral 5-ASA. The mean age of participants was 13.4 years (range 4 to 17). 53.6% (37) of participants were female. The mean weight was 52.4 kg (range 16 to 107). Baseline disease characteristics for the overall golimumab population were representative of paediatric patients with moderately to severely active UC.

In the Induction Phase (week 0 to week 6), children received body weight-based golimumab SC, at weeks 0 and 2. Children with body weight ≥ 45 kg received fixed induction doses of 200 mg SC at week 0 and 100 mg at week 2. Children with body weight < 45 kg received body-surface area-adjusted induction doses of 120 mg/m^2 SC (up to a maximum of 200 mg) at week 0 and 60 mg/m^2 SC (up to a maximum of 100 mg) at week 2. At week 6, children were evaluated for efficacy and safety.

In the Maintenance Phase (week 6 through week 54), children in clinical response to golimumab (a decrease from baseline in the full Mayo score of ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1 using the local read for the endoscopy subscore) continued to receive SC golimumab 100 mg (children weighing ≥ 45 kg) or 60 mg/m^2 (children weighing < 45 kg) every 4 weeks through week 50. For children with no clinical response at week 6, additional doses at week 6 and week 10 could have been given, followed by a response assessment at week 14 to determine if the children continued with golimumab every 4 weeks through week 50. Of the 41 children who entered the maintenance phase, 39 children remained in the study at week 54 (had a full Mayo score efficacy determination).

The primary endpoint of clinical remission as measured by the Mayo score was defined as a Mayo score ≤ 2 points, with no individual subscore > 1 (based on Mayo endoscopy subscore assigned by the local endoscopist). Overall, 22 (31.9%) of children showed clinical remission at week 6. At week 54, 31.7% of week 6 clinical responders were in clinical remission.

Table 7
Key efficacy outcomes from PURSUIT 2 – Induction and PURSUIT 2 - Maintenance

PURSUIT 2 - Induction	
Primary Endpoint	**Simponi N=69**
Subjects in clinical remission as assessed by the Mayo score at week 6[a]	22 (31.9%)
Major Secondary Endpoints	

Subjects in clinical response at week 6[b]	39 (56.5%)
Subjects with endoscopic healing at week 6[c]	28 (40.6%)
PURSUIT 2 – Maintenance	
Major Secondary Endpoints	**Simponi N=41**
Subjects in clinical remission at week 54 as assessed by the Mayo score[a,e]	13 (31.7%)
Subjects with endoscopic healing at week 54[c]	15 (36.6%)
Subjects in clinical remission at week 54 as assessed by the Mayo score, for participants who are in clinical remission at Week 6[a,d,e]	12 (54.5%)

N = number of patients

[a] Clinical remission is defined as a Mayo score ≤ 2 points, with no individual subscore > 1.

[b] Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

[c] Endoscopic healing is defined as an endoscopy subscore of 0 or 1 based on local endoscopy.

[d] Denominator is subjects who were in clinical remission at Week 6.

[e] Subjects who had a missing endoscopy score at Week 54 were considered not to be in clinical remission.

Adult ulcerative colitis

The efficacy of Simponi was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients.

The induction study (PURSUIT-Induction) evaluated patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) who had an inadequate response to or failed to tolerate conventional therapies, or were corticosteroid dependent. In the dose confirming portion of the study, 761 patients were randomised to receive either 400 mg Simponi SC at week 0 and 200 mg at week 2, 200 mg Simponi SC at week 0 and 100 mg at week 2, or placebo SC at weeks 0 and 2. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. The efficacy of Simponi through week 6 was assessed in this study.

The results of the maintenance study (PURSUIT-Maintenance) were based on evaluation of 456 patients who achieved clinical response from previous induction with Simponi. Patients were randomised to receive Simponi 50 mg, Simponi 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, and/or immunomodulatory agents were permitted. Corticosteroids were to be tapered at the start of the maintenance study. The efficacy of Simponi through week 54 was assessed in this study. Patients who completed the maintenance study through week 54 continued treatment in a study extension, with efficacy evaluated through week 216. Efficacy evaluation in the study extension was based on changes in corticosteroid use, Physician's Global Assessment (PGA) of disease activity, and improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire (IBDQ).

Table 8
Key efficacy outcomes from PURSUIT - Induction and PURSUIT - Maintenance

PURSUIT-Induction		
	Placebo N = 251	**Simponi 200/100 mg** N = 253
Percentage of patients		
Patients in clinical response at week 6[a]	30%	51%**
Patients in clinical remission at week 6[b]	6%	18%**
Patients with mucosal healing at week 6[c]	29%	42%*

PURSUIT-Maintenance			
	Placebo[d] N = 154	**Simponi 50 mg** N = 151	**Simponi 100 mg** N = 151
Percentage of patients			
Maintenance of response (Patients in clinical response through week 54)[e]	31%	47%*	50%**
Sustained remission (Patients in clinical remission at both week 30 and week 54)[f]	16%	23%[g]	28%*

N = number of patients

** $p \leq 0.001$

* $p \leq 0.01$

[a] Defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

[b] Defined as a Mayo score ≤ 2 points, with no individual subscore > 1

[c] Defined as 0 or 1 on the endoscopy subscore of the Mayo score.

[d] Simponi induction only.

[e] Patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). Therefore, a patient who maintained response was in a state of continuous clinical response at each evaluation through week 54.

[f] A patient had to be in remission at both weeks 30 and 54 (without demonstrating a loss of response at any time point through week 54) to achieve durable remission.

[g] In patients weighing less than 80 kg, a greater proportion of patients who received 50 mg maintenance therapy showed sustained clinical remission compared with those who received placebo.

More Simponi-treated patients demonstrated sustained mucosal healing (patients with mucosal healing at both week 30 and week 54) in the 50 mg group (42%, nominal $p < 0.05$) and 100 mg group (42%, $p < 0.005$) compared with patients in the placebo group (27%).

Among the 54% of patients (247/456) who were receiving concomitant corticosteroids at the start of PURSUIT-Maintenance, the proportion of patients who maintained clinical response through week 54 and were not receiving concomitant corticosteroids at week 54 was greater in the 50 mg group (38%, 30/78) and 100 mg group (30%, 25/82) compared with the placebo group (21%, 18/87). The proportion of patients who eliminated corticosteroids by week 54 was greater in the 50 mg group (41%, 32/78) and 100 mg group (33%, 27/82) compared with the placebo group (22%, 19/87). Among patients who entered the study extension, the proportion of subjects who remained corticosteroid free was generally maintained through week 216.

Patients who did not achieve clinical response at week 6 in the PURSUIT-Induction studies were dosed Simponi 100 mg every 4 weeks in the PURSUIT-Maintenance study. At week 14, 28% of these patients achieved response defined by partial Mayo score (decreased by ≥ 3 points compared with start of induction). At week 54, the clinical outcomes observed in these patients were similar to the clinical outcomes reported for the patients achieving clinical response at week 6.

At week 6, Simponi significantly improved quality of life as measured by change from baseline in a disease specific measure, IBDQ (inflammatory bowel disease questionnaire). Among patients who received Simponi maintenance treatment, the improvement in quality of life as measured by IBDQ was maintained through week 54.

Approximately 63% of patients who were receiving Simponi at the beginning of the study extension (week 56), remained on treatment through the end of the study (last golimumab administration at week 212).

Immunogenicity

Across the Phase III RA, PsA and AS studies through week 52, antibodies to golimumab were detected by the enzyme immunoassay (EIA) method in 5% (105/2062) of golimumab treated patients and, where tested, nearly all antibodies were neutralising *in vitro*. Similar rates were shown across

rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without MTX (approximately 3% [41/1235] versus 8% [64/827], respectively).

In nr-Axial SpA, antibodies to golimumab were detected in 7% (14/193) of golimumab treated patients through week 52 by the EIA method.

In the Phase II and III UC studies through week 54, antibodies to golimumab were detected by the EIA method in 3% (26/946) of golimumab treated patients. Sixty-eight percent (21/31) of antibody-positive patients had neutralising antibodies *in vitro*. Treatment with concomitant immunomodulators (azathioprine, 6-mercaptopurine and MTX) resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without immunomodulators (1% (4/308) versus 3% (22/638), respectively). Of patients that continued in the study extension and had evaluable samples through week 228, antibodies to golimumab were detected in 4% (23/604) of golimumab treated patients. Eighty-two percent (18/22) of antibody-positive patients had neutralising antibodies *in vitro*.

A drug-tolerant EIA method was used in the pJIA study for the detection of antibodies to golimumab. Due to the higher sensitivity and the improved drug tolerance, a higher incidence of antibodies to golimumab was expected to be detected with the drug-tolerant EIA method compared to the EIA method. In the Phase III pJIA study through week 48, antibodies to golimumab were detected by the drug-tolerant EIA method in 40% (69/172) of golimumab treated children of which a majority had a titre lower than 1:1000. An effect on serum golimumab concentrations was seen at titres of > 1:100 while an effect on efficacy was not seen until titres of > 1:1000, though the numbers of children with titres of > 1:1000 were low (N = 8). Among the children who tested positive for antibodies to golimumab, 39% (25/65) had neutralising antibodies. The higher incidence of antibodies with the drug-tolerant EIA method, because they were mainly low titre antibodies, did not have an apparent impact on drug levels, efficacy and safety and therefore does not represent any new safety signal.

The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.8). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

Because immunogenicity analyses are product- and assay-specific, comparison of antibody rates with those from other products is not appropriate.

In the Phase III paediatric UC trial, 22% (15/69) of Simponi-treated patients were positive for antibodies to golimumab through the final safety visit using the drug-tolerant EIA method. Most patients with antibodies had low titres. The incidence of antibodies to golimumab was comparable between paediatric and adult patients with UC. UC patients who developed antibodies to golimumab, generally had lower trough steady-state serum concentrations of golimumab.

5.2 Pharmacokinetic properties

Absorption
Following a single subcutaneous administration of golimumab to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A subcutaneous injection of 50 mg golimumab to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/mL.

Following a single subcutaneous injection of 100 mg, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since golimumab exhibited approximately dose proportional PK following a subcutaneous administration, the absolute bioavailability of a golimumab 50 mg or 200 mg dose is expected to be similar.

Distribution
Following a single IV administration, the mean volume of distribution was 115 ± 19 mL/kg.

Elimination
The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg. Terminal half-life value was estimated to be approximately 12 ± 3 days in healthy subjects and similar values were observed in patients with RA, PsA, AS, or UC.

When 50 mg golimumab was administered subcutaneously to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by week 12. With concomitant use of MTX, treatment with 50 mg golimumab subcutaneously every 4 weeks resulted in a mean (± standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 μg/mL in patients with active PsA and approximately 0.8 ± 0.4 μg/mL in patients with AS. Steady-state trough mean serum golimumab concentrations in patients with nr-Axial SpA were similar to those observed in patients with AS following subcutaneous administration of 50 mg golimumab every 4 weeks.

Patients with RA, PsA or AS who did not receive concomitant MTX had approximately 30% lower steady-state trough concentrations of golimumab than those who received golimumab with MTX. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. However, population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

Following induction doses of 200 mg and 100 mg golimumab at week 0 and 2, respectively, and maintenance doses of 50 mg or 100 mg golimumab subcutaneously every 4 weeks thereafter to patients with UC, serum golimumab concentrations reached steady state approximately 14 weeks after the start of therapy. Treatment with 50 mg or 100 mg golimumab subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 0.9 ± 0.5 μg/mL and 1.8 ± 1.1 μg/mL, respectively.

In UC patients treated with 50 mg or 100 mg golimumab subcutaneously every 4 weeks, concomitant use of immunomodulators did not have a substantial effect on steady-state trough levels of golimumab.

Patients who developed antibodies to golimumab generally had low trough steady-state serum concentrations of golimumab (see section 5.1).

Linearity
Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose. Following a single SC dose in healthy subjects, approximately dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg.

Effect of weight on pharmacokinetics
There was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

Paediatric population
Polyarticular juvenile idiopathic arthritis
The pharmacokinetics of golimumab were determined in 173 children with pJIA with an age range from 2 to 17 years of age. In the pJIA study, children who received golimumab 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks, had median steady-state trough golimumab concentrations which were similar across different age groups, and which were also similar to or slightly higher than those seen in adult RA patients who received 50 mg golimumab every 4 weeks.

Population pharmacokinetic/pharmacodynamic modelling and simulation in children with pJIA confirmed the relationship between golimumab serum exposures and clinical efficacy and supports the dosing regimen of golimumab 30 mg/m^2 every 4 weeks in children with pJIA.

Ulcerative colitis
The pharmacokinetics of golimumab were similar between paediatric and adult patients with ulcerative colitis. Population pharmacokinetics confirmed that the recommended dosing regimen for Simponi resulted in similar or slightly higher serum golimumab exposure in paediatric subjects as compared to adults across the body weight range.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

No mutagenicity studies, animal fertility studies nor long-term carcinogenic studies have been conducted with golimumab.

In a fertility and general reproductive function study in mouse, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, the number of pregnant mice was reduced. It is not known whether this finding was due to effects on the males and/or the females. In a developmental toxicity study conducted in mice following administration of the same analogous antibody, and in cynomolgus monkeys using golimumab, there was no indication of maternal toxicity, embryotoxicity or teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect it from light.
Simponi may be stored at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 30 days from the date removed from the refrigerator).

Once Simponi has been stored at room temperature, it should not be returned to refrigerated storage. Simponi must be discarded if not used within the 30 days of room temperature storage.

6.5 Nature and contents of container

Simponi 45 mg/0.45 mL solution for injection
0.45 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex) in a pre-filled pen. Each pre-filled pen can deliver 0.1 mL to 0.45 mL in increments of 0.05 mL.
Pack size of 1 pre-filled pen.

6.6 Special precautions for disposal and other handling

Simponi is supplied in a single use pre-filled pen. Each pack is provided with instructions for use that fully describe the use of the pen. After removing the pre-filled pen from the refrigerator it should be allowed to reach room temperature by waiting for 30 minutes, before injecting Simponi. The pen should not be shaken.

The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for solutions containing protein. Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

Comprehensive instructions for the preparation and administration of Simponi in a pre-filled pen are included in the pack.

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/009 1 pre-filled pen

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 October 2009
Date of latest renewal: 19 June 2014

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

Simponi 50 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 0.5 mL pre-filled syringe contains 50 mg of golimumab*.

* Human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology.

Excipients with known effect
Each pre-filled syringe contains 20.5 mg sorbitol (E420) per 50 mg dose.

Each pre-filled syringe contains 0.075 mg of polysorbate 80 (E433) per 50 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)
Simponi, in combination with methotrexate (MTX), is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

Simponi, in combination with MTX, 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
Polyarticular juvenile idiopathic arthritis (pJIA)
Simponi in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Psoriatic arthritis (PsA)
Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Simponi has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Axial spondyloarthritis
Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)
Simponi is indicated for the treatment of adults with severe, active 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, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)
Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis (pUC)
Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients 2 years of age and older with a body weight of at least 15 kg, who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

4.2 Posology and method of administration

Treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis. Patients treated with Simponi should be given the Patient Card.

Posology

Rheumatoid arthritis
Simponi 50 mg given once a month, on the same date each month.
Simponi should be given concomitantly with MTX.

Psoriatic arthritis, ankylosing spondylitis, or non-radiographic axial spondyloarthritis
Simponi 50 mg given once a month, on the same date each month.

For all of the above indications, available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Patients with body weight greater than 100 kg
For all of the above indications, in patients with RA, PsA, AS, or nr-Axial SpA with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse reactions with the 100 mg dose compared with the 50 mg dose (see section 4.8). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

Polyarticular juvenile idiopathic arthritis
Simponi 50 mg administered once a month, on the same date each month, for children with a body weight of at least 40 kg. A 45 mg/0.45 mL pre-filled pen is available for administration to children with polyarticular juvenile idiopathic arthritis weighing less than 40 kg.

Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in children who show no evidence of therapeutic benefit within this time period.

Adult ulcerative colitis
Patients with body weight less than 80 kg
Simponi given as an initial dose of 200 mg, followed by 100 mg at week 2. Patients who have an adequate response should receive 50 mg at week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter (see section 5.1).

Patients with body weight greater than or equal to 80 kg
Simponi given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter (see section 5.1).

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Paediatric ulcerative colitis (pUC)
The recommended dose of Simponi for patients from 2 to 17 years of age with ulcerative colitis is based on body weight (Table 1). Simponi is administered via subcutaneous injection.

Table 1: Simponi dose for paediatric patients with ulcerative colitis

Patient weight	Induction Dose	Maintenance Dose Starting at Week 6	Optional Maintenance Dose reduction*
≥80 kg	• 200 mg at week 0 and • 100 mg at week 2	• 100 mg every four weeks	Not applicable
≥40 kg to <80 kg	• 200 mg at week 0 and • 100 mg at week 2	• 100 mg every four weeks	• 50 mg every four weeks
≥15 kg to <40 kg	• 100 mg at week 0 and • 50 mg at week 2	• 50 mg every four weeks	• 25 mg every four weeks

* The physician may consider decreasing the maintenance dose for patients who are in remission at or after week 54.

For the posology and administration of 25 mg of golimumab, refer to section 4.2 of the 45 mg/0.45 mL solution for injection in pre-filled pen SmPC.
For the posology and administration of 100 mg of golimumab, refer to section 4.2 of the 100 mg solution for injection in pre-filled syringe SmPC.
Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in children who show no evidence of therapeutic benefit within this time period.

Missed dose
If a patient forgets to inject Simponi on the planned date, the forgotten dose should be injected as soon as the patient remembers. Patients should be instructed not to inject a double dose to make up for the forgotten dose.

The next dose should be administered based on the following guidance:
- if the dose is less than 2 weeks late, the patient should inject the forgotten dose and stay on the original schedule.
- if the dose is more than 2 weeks late, the patient should inject the forgotten dose and a new schedule should be established from the date of this injection.

Special populations
Elderly (≥ 65 years)
No dose adjustment is required in the elderly.

Renal and hepatic impairment
Simponi has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of Simponi in patients aged less than 18 for indications other than pJIA and pUC have not been established. No data are available.
There is no relevant use of Simponi in children aged less than 2 years in pJIA or pUC.

Method of administration
Simponi is for subcutaneous use. After proper training in subcutaneous injection technique, patients may self-inject if their physician determines that this is appropriate, with medical follow-up as necessary. Patients should be instructed to inject the full amount of Simponi according to the comprehensive instructions for use provided in the package leaflet. If multiple injections are required, the injections should be administered at different sites on the body. Each pre-filled syringe is for single use in a single patient, and should be discarded immediately after use.

For administration instructions, see section 6.6.

4.3 Contraindications

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

Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate or severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Patients must be monitored closely for infections including tuberculosis before, during and after treatment with golimumab. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. Further treatment with golimumab must not be given if a patient develops a serious infection or sepsis (see section 4.3).

Golimumab should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of golimumab in patients with a chronic infection or a history of recurrent infection. Patients should be advised of, and avoid exposure to, potential risk factors for infection as appropriate.

Patients taking TNF-blockers are more susceptible to serious infections.
Bacterial (including sepsis and pneumonia), mycobacterial (including TB), invasive fungal and opportunistic infections, including fatalities, have been reported in patients receiving golimumab. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with golimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of golimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of golimumab treatment should be carefully considered before initiation of golimumab therapy. In at-risk patients treated with golimumab, an invasive fungal infection should be suspected if they develop a serious systemic illness. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections, if feasible.

Tuberculosis

There have been reports of tuberculosis in patients receiving golimumab. It should be noted that in the majority of these reports, tuberculosis was extrapulmonary presenting as either local or disseminated disease.

Before starting treatment with golimumab, 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 or blood 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, golimumab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of golimumab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of golimumab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of golimumab. Use of anti-tuberculosis therapy should also be considered before the initiation of golimumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Cases of active tuberculosis have occurred in patients treated with golimumab during and after treatment for latent tuberculosis. Patients receiving golimumab should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

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 golimumab treatment.

Hepatitis B virus reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including golimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with golimumab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with golimumab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, golimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Malignancies and lymphoproliferative disorders
The potential role of TNF-blocking therapy in the development of malignancies is not known. Based on the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

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

Lymphoma and leukaemia
In the controlled portions of clinical trials of all the TNF-blocking agents including golimumab, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the Simponi Phase IIb and Phase III clinical trials in RA, PsA and AS, the incidence of lymphoma in golimumab-treated patients was higher than expected in the general population. Cases of leukaemia have been reported in patients treated with golimumab. 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.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with other TNF-blocking agents (see section 4.8). This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of cases have occurred in adolescent and young adult males with nearly all on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) for inflammatory bowel disease. The potential risk with the combination of AZA or 6-MP and golimumab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Malignancies other than lymphoma
In the controlled portions of the Simponi Phase IIb and Phase III clinical trials in RA, PsA, AS, and UC, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups.

Colon dysplasia/carcinoma
It is not known if golimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with golimumab, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

In an exploratory clinical trial evaluating the use of golimumab in patients with severe persistent asthma, more malignancies were reported in patients treated with golimumab compared with control patients (see section 4.8). The significance of this finding is unknown.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with an increased risk of malignancy due to heavy smoking.

Skin cancers
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents, including golimumab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

Congestive heart failure (CHF)
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including golimumab. Some cases had a fatal outcome. In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to CHF have been observed. Golimumab has not been studied in patients with CHF. Golimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and golimumab must be discontinued in patients who develop new or worsening symptoms of heart failure (see section 4.3).

Neurological events
Use of TNF-blocking agents, including golimumab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy. Discontinuation of golimumab should be considered if these disorders develop (see section 4.8).

Surgery
There is limited safety experience of golimumab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on golimumab should be closely monitored for infections, and appropriate actions should be taken.

Immunosuppression
The possibility exists for TNF-blocking agents, including golimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Autoimmune processes
The relative deficiency of TNF-α caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with golimumab and is positive for antibodies against double-stranded DNA, treatment with golimumab should be discontinued (see section 4.8).

Haematologic reactions
There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anaemia, and thrombocytopenia in patients receiving TNF-blockers, including golimumab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of golimumab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent administration of TNF-antagonists and anakinra
Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. The combination of golimumab and anakinra is not recommended.

Concurrent administration of TNF-antagonists and abatacept
In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of golimumab and abatacept is not recommended.

Concurrent administration with other biological therapeutics
There is insufficient information regarding the concomitant use of golimumab with other biological therapeutics used to treat the same conditions as golimumab. The concomitant use of golimumab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs
Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Vaccinations/therapeutic infectious agents
Patients treated with golimumab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6). In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g. BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with golimumab.

Allergic reactions
In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following golimumab administration. Some of these reactions occurred after the first administration of golimumab. If an anaphylactic reaction or other serious allergic reactions occur, administration of golimumab should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity
The needle cover on the pre-filled pen or the pre-filled syringe is manufactured from dry natural rubber containing latex, and may cause allergic reactions in individuals sensitive to latex.

Special populations

Elderly (≥ 65 years)
In the Phase III studies in RA, PsA, AS, and UC, no overall differences in adverse events (AEs), serious adverse events (SAEs), and serious infections in patients age 65 or older who received golimumab 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. There were no patients age 45 and over in the nr-Axial SpA study.

Renal and hepatic impairment
Specific studies of golimumab have not been conducted in patients with renal or hepatic impairment. Golimumab should be used with caution in subjects with impaired hepatic function (see section 4.2).

Paediatrics
Vaccinations
If possible, it is recommended that prior to initiating golimumab therapy, paediatric patients be brought up to date with all immunisations in agreement with current immunisation guidelines (see Vaccinations/therapeutic infectious agents above).

Excipients with known effect
Sorbitol
Simponi contains sorbitol (E420). In patients with rare hereditary problems of fructose intolerance, the additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account (see section 2).

Polysorbate 80
Simponi contains 0.075 mg of polysorbate 80 (E433) in each pre-filled syringe. Polysorbates may cause allergic reactions (see section 2).

Potential for medication errors
Simponi is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in the posology (see section 4.2). Care should be taken to provide the right strength to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with other biological therapeutics
The combination of golimumab with other biological therapeutics used to treat the same conditions as golimumab, including anakinra and abatacept is not recommended (see section 4.4).

Live vaccines/therapeutic infectious agents
Live vaccines should not be given concurrently with golimumab (see sections 4.4 and 4.6).

Therapeutic infectious agents should not be given concurrently with golimumab (see section 4.4).

Methotrexate
Although concomitant use of MTX results in higher steady-state trough concentrations of golimumab in patients with RA, PsA or AS, the data do not suggest the need for dose adjustment of either golimumab or MTX (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last golimumab treatment.

Pregnancy
There is a moderate amount (approximately 400) of prospectively collected pregnancies exposed to golimumab resulting in live birth with known outcomes, including 220 pregnancies exposed during the first trimester. In a population-based study from Northern Europe including 131 pregnancies (and 134 infants), there were 6/134 (4.5%) events of major congenital anomalies following *in utero* exposure to Simponi vs 599/10,823 (5.5%) events for non-biologic systemic therapy compared to 4.6% in the general population of the study. Confounder-adjusted odds ratios were OR 0.79 (95% CI 0.35-1.81) for Simponi vs. non-biologic systemic therapy and OR 0.95 (95% CI 0.42-2.16) for Simponi vs. the general population, respectively.

Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The available clinical experience is limited. Golimumab should only be used during pregnancy if clearly needed.

Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see sections 4.4 and 4.5).

Breast-feeding
It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Golimumab was shown to pass over to breast milk in monkeys, and because human immunoglobulins are excreted in milk, women must not breast feed during and for at least 6 months after golimumab treatment.

Fertility
No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, showed no relevant effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Simponi has minor influence on the ability to drive and use machines. Dizziness may however occur following administration of Simponi (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
In the controlled period of the pivotal trials in RA, PsA, AS, nr-Axial SpA, and UC, upper respiratory tract infection was the most common adverse reaction (AR) reported in 12.6% of golimumab-treated patients compared with 11.0% of control patients. The most serious ARs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome), haematologic reactions, serious systemic hypersensitivity (including anaphylactic reaction), vasculitis, lymphoma and leukaemia (see section 4.4).

Tabulated list of adverse reactions
ARs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed in Table 2. Within the designated system organ classes, the ARs are listed under headings of frequency and using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2
Tabulated list of ARs

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)
Common:	Bacterial infections (such as cellulitis), lower respiratory tract infection (such as pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess
Uncommon:	Sepsis including septic shock, pyelonephritis

Rare:	Tuberculosis, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), hepatitis B reactivation, bacterial arthritis, infective bursitis
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia, melanoma, Merkel cell carcinoma
Not known:	Hepatosplenic T-cell lymphoma*, Kaposi's sarcoma
Blood and lymphatic system disorders	
Common:	Leukopenia (including neutropenia), anaemia
Uncommon:	Thrombocytopenia, pancytopenia
Rare:	Aplastic anaemia, agranulocytosis
Immune system disorders	
Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis
Endocrine disorders	
Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders	
Uncommon:	Blood glucose increased, lipids increased
Psychiatric disorders	
Common:	Depression, insomnia
Nervous system disorders	
Common:	Dizziness, headache, paraesthesia
Uncommon:	Balance disorders
Rare:	Demyelinating disorders (central and peripheral), dysgeusia
Eye disorders	
Uncommon:	Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritus and irritation)
Cardiac disorders	
Uncommon:	Arrhythmia, ischaemic coronary artery disorders
Rare:	Congestive heart failure (new onset or worsening)
Vascular disorders	
Common:	Hypertension
Uncommon:	Thrombosis (such as deep venous and aortic), flushing
Rare:	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	Asthma and related symptoms (such as wheezing and bronchial hyperactivity)
Uncommon:	Interstitial lung disease
Gastrointestinal disorders	
Common:	Dyspepsia, gastrointestinal and abdominal pain, nausea, gastrointestinal inflammatory disorders (such as gastritis and colitis), stomatitis
Uncommon:	Constipation, gastro-oesophageal reflux disease
Hepatobiliary disorders	
Common:	Alanine aminotransferase increased, aspartate aminotransferase increased
Uncommon:	Cholelithiasis, hepatic disorders

Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia, dermatitis
Uncommon:	Bullous skin reactions, psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria
Rare:	Lichenoid reactions, skin exfoliation, vasculitis (cutaneous)
Not known:	Worsening of symptoms of dermatomyositis
Musculoskeletal and connective tissue disorders	
Rare:	Lupus-like syndrome
Renal and urinary disorders	
Rare:	Bladder disorders, renal disorders
Reproductive system and breast disorders	
Uncommon:	Breast disorders, menstrual disorders
General disorders and administration site conditions	
Common:	Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia), chest discomfort
Rare:	Impaired healing
Injury, poisoning and procedural complications	
Common:	Bone fractures

* Observed with other TNF-blocking agents.

Throughout this section, median duration of follow-up (approximately 4 years) is generally presented for all golimumab use. Where golimumab use is described by dose, the median duration of follow-up varies (approximately 2 years for 50 mg dose, approximately 3 years for 100 mg dose) as patients may have switched between doses.

Description of selected adverse reactions

Infections
In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of golimumab-treated patients (incidence per 100 subject-years: 60.8; 95% CI: 55.0, 67.1) compared with 11.0% of control patients (incidence per 100 subject-years: 54.5; 95% CI: 46.1, 64.0). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 4 years, the incidence per 100 subject-years of upper respiratory tract infections was 34.9 events; 95% CI: 33.8, 36.0 for golimumab treated patients.

In the controlled period of pivotal trials, infections were observed in 23.0% of golimumab-treated patients (incidence per 100 subject-years: 132.0; 95% CI: 123.3, 141.1) compared with 20.2% of control patients (incidence per 100 subject-years: 122.3; 95% CI: 109.5, 136.2). In controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per 100 subject-years of infections was 81.1 events; 95% CI: 79.5, 82.8 for golimumab treated patients.

In the controlled period of RA, PsA, AS, and nr-Axial SpA trials, serious infections were observed in 1.2% of golimumab-treated patients and 1.2% of control-treated patients. The incidence of serious infections per 100 subject-years of follow-up in the controlled period of RA, PsA, AS, and nr-Axial SpA trials was 7.3; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 2.9; 95% CI: 1.2, 6.0 for the golimumab 50 mg group and 3.6; 95% CI: 1.5, 7.0 for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of golimumab-treated patients compared with 1.5% of control-treated patients. Serious infections observed in golimumab-treated patients included tuberculosis, bacterial infections including sepsis and pneumonia, invasive fungal infections and other opportunistic infections. Some of these infections have been fatal. In the controlled and uncontrolled portions of the pivotal trials with a median follow-up of up to

3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 4.1; 95% CI: 3.6, 4.5, in patients receiving golimumab 100 mg and 2.5; 95% CI: 2.0, 3.1, in patients receiving golimumab 50 mg.

Malignancies
Lymphoma
The incidence of lymphoma in golimumab-treated patients during the pivotal trials was higher than expected in the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Lymphoma was diagnosed in 11 subjects (1 in the golimumab 50 mg treatment groups and 10 in the golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.03 (0.00, 0.15) and 0.13 (0.06, 0.24) events for golimumab 50 mg and 100 mg respectively and 0.00 (0.00, 0.57) events for the placebo. The majority of lymphomas occurred in study GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease (see section 4.4).

Malignancies other than lymphoma
In the controlled periods of pivotal trials and through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar to the general population.

In the controlled and uncontrolled periods of pivotal trials with a median follow-up of up to 3 years, non-melanoma skin cancer was diagnosed in 5 placebo-treated, 10 golimumab 50 mg-treated and 31 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.36 (0.26, 0.49) for combined golimumab and 0.87 (0.28, 2.04) for placebo.

In the controlled and uncontrolled period of pivotal trials with a median follow-up of up to 3 years, malignancies besides melanoma, non-melanoma skin cancer and lymphoma were diagnosed in 5 placebo-treated, 21 golimumab 50 mg-treated and 34 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.48 (0.36, 0.62) for combined golimumab and 0.87 (0.28, 2.04) for placebo (see section 4.4).

Cases reported in clinical studies in asthma
In an exploratory clinical study, patients with severe persistent asthma received a golimumab loading dose (150% of the assigned treatment dose) subcutaneously at week 0 followed by golimumab 200 mg, golimumab 100 mg or golimumab 50 mg every 4 weeks subcutaneously through week 52. Eight malignancies in the combined golimumab treatment group (n = 230) and none in the placebo treatment group (n = 79) were reported. Lymphoma was reported in 1 patient, non-melanoma skin cancer in 2 patients, and other malignancies in 5 patients. There was no specific clustering of any type of malignancy.

During the placebo-controlled portion of the study, the incidence (95% CI) of all malignancies per 100 subject-years of follow-up was 3.19 (1.38, 6.28) in the golimumab group. In this study, the incidence (95% CI) per 100 subject-years of follow-up in golimumab-treated subjects was 0.40 (0.01, 2.20) for lymphoma, 0.79 (0.10, 2.86) for non-melanoma skin cancers, and 1.99 (0.64, 4.63) for other malignancies. For placebo subjects, the incidence (95% CI) per 100 subject-years of follow-up of these malignancies was 0.00 (0.00, 2.94). The significance of this finding is unknown.

Neurological events
In the controlled and uncontrolled periods of the pivotal trials with a median follow-up of up to 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg (see section 4.4).

Liver enzyme elevations
In the controlled period of RA and PsA pivotal trials, mild ALT elevations (> 1 and < 3 x upper limit of normal (ULN)) occurred in similar proportions of golimumab and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS and nr-Axial SpA studies, more golimumab-treated patients (26.9%) than control patients (10.6%) had mild ALT elevations. In the controlled and uncontrolled periods of the RA and PsA pivotal trials, with a median follow-up of approximately 5 years, the incidence of mild ALT elevations was similar in golimumab-treated and control patients in RA and PsA studies. In the controlled period of the UC pivotal trials of golimumab induction, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of golimumab-treated and control patients (8.0% to 6.9%, respectively). In controlled and uncontrolled periods of the UC pivotal trials with a median follow-up of approximately 2 years, the proportion of patients with mild ALT elevations was 24.7% in patients receiving golimumab during the maintenance portion of the UC study.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5 x ULN were uncommon and seen in more golimumab-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. In the controlled and uncontrolled periods of RA, PsA and AS pivotal trials, with a median follow-up of 5 years, the incidence of ALT elevations ≥ 5 x ULN was similar in both golimumab-treated and control patients. In general these elevations were asymptomatic and the abnormalities decreased or resolved with either continuation or discontinuation of golimumab or modification of concomitant medicinal products. No cases were reported in the controlled and uncontrolled periods of the nr-Axial SpA study (up to 1 year). In the controlled periods of the pivotal UC trials, of golimumab induction, ALT elevations ≥ 5 x ULN occurred in similar proportions of golimumab-treated patients compared to placebo-treated patients (0.3% to 1.0%, respectively). In the controlled and uncontrolled periods of the pivotal UC trials with a median follow-up of approximately 2 years, the proportion of patients with ALT elevations ≥ 5 x ULN was 0.8% in patients receiving golimumab during the maintenance portion of the UC study.

Within the RA, PsA, AS, and nr-Axial SpA pivotal trials, one patient in an RA trial with pre-existing liver abnormalities and confounding medicinal products treated with golimumab developed non-infectious fatal hepatitis with jaundice. The role of golimumab as a contributing or aggravation factor cannot be excluded.

Injection site reactions
In the controlled periods of pivotal trials, 5.4% of golimumab-treated patients had injection site reactions compared with 2.0% in control patients. The presence of antibodies to golimumab may increase the risk of injection site reactions. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

In controlled Phase IIb and/or III trials in RA, PsA, AS, nr-Axial SpA, severe persistent asthma, and Phase II/III trials in UC, no patients treated with golimumab developed anaphylactic reactions.

Autoimmune antibodies
In the controlled and uncontrolled periods of pivotal trials through 1 year of follow-up, 3.5% of golimumab-treated patients and 2.3% of control patients were newly ANA-positive (at titres of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients anti-dsDNA negative at baseline was 1.1%.

Paediatric population
Polyarticular juvenile idiopathic arthritis
The safety of golimumab has been studied in a Phase III study of 173 pJIA patients from 2 to 17 years of age. The average follow-up was approximately two years. In this study, the type and frequency of adverse events reported were generally similar to those seen in adult RA studies.

Ulcerative colitis
The safety of golimumab has been studied in a Phase III study of 69 patients from 4 to 17 years of age with moderately to severely active ulcerative colitis. In this study, adverse reactions observed were consistent with the established safety profile of golimumab in adult patients with UC.

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

Single doses up to 10 mg/kg intravenously have been administered in a clinical study without dose-limiting toxicity. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors, ATC code: L04AB06

Mechanism of action
Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors.

Pharmacodynamic effects
The binding of human TNF by golimumab was shown to neutralise TNF-α-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. *In vitro*, TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab.

Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with Simponi resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix-metalloproteinase (MMP)-3 and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNF-α were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients. These changes were observed at the first assessment (week 4) after the initial Simponi administration and were generally maintained through week 24.

Clinical efficacy

Adult rheumatoid arthritis
The efficacy of Simponi was demonstrated in three multi-centre, randomised, double-blind, placebo-controlled studies in over 1500 patients ≥ 18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening. Patients had at least 4 swollen and 4 tender joints. Simponi or placebo were subcutaneously administered every 4 weeks.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi

100 mg + placebo. Patients receiving placebo + MTX were switched to Simponi 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

GO-AFTER evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomised to receive placebo, Simponi 50 mg, or Simponi 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Simponi 50 mg + MTX.

In GO-FORWARD, the (co-) primary endpoints were the percentage of patients achieving an ACR 20 response at week 14 and the improvement from baseline in Health Assessment Questionnaire (HAQ) at week 24. In GO-AFTER, the primary endpoint was the percentage of patients achieving an ACR 20 response at week 14. In GO-BEFORE, the co-primary endpoints were the percentage of patients achieving ACR 50 response at week 24 and the change from baseline in the van der Heijde-modified Sharp (vdH-S) score at week 52. In addition to the primary endpoint(s), additional assessments of the impact of Simponi treatment on the signs and symptoms of arthritis, radiographic response, physical function and health-related quality of life were performed.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens with concomitant MTX, through week 104 in GO-FORWARD and GO-BEFORE and through week 24 in GO-AFTER. In each of the RA studies by study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms
Key ACR results for the Simponi 50 mg dose at weeks 14, 24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 3 and are described below. Responses were observed at the first assessment (week 4) after the initial Simponi administration.

In GO-FORWARD, among 89 subjects randomised to Simponi 50 mg + MTX, 48 were still on this treatment at week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving Simponi than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 3
Key efficacy outcomes from the controlled portions of GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	Simponi 50 mg + MTX	Placebo	Simponi 50 mg	Placebo + MTX	Simponi 50 mg + MTX
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA
Week 24	28%	60%*	16%	31% p = 0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p = 0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p = 0.008	2%	10% p = 0.005	NA	NA
Week 24	5%	20%*	2%	9% p = 0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.
* $p \leq 0.001$
NA: Not Applicable

In GO-BEFORE the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Simponi 50 and 100 mg + MTX groups vs MTX alone for ACR50) was not statistically significant at week 24 ($p = 0.053$). At week 52 in the overall population, the percentage of patients in the Simponi 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 3). Additional analyses were performed in subsets representative of the indicated population of patients with severe, active and progressive RA. A generally greater effect of Simponi 50 mg + MTX versus MTX alone was demonstrated in the indicated population compared with the overall population.

In GO-FORWARD and GO-AFTER, clinically meaningful and statistically significant responses in Disease Activity Scale (DAS)28 were observed at each prespecified time point, at week 14 and at week 24 ($p \leq 0.001$). Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 responses were similar from week 104 through week 256.

In GO-BEFORE, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At week 52, 15% of patients in the Simponi 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group ($p = 0.018$). Among 159 subjects randomised to Simponi 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response were observed from week 104 through week 256.

Radiographic response
In GO-BEFORE the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space

narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Simponi 50 mg dose at week 52 are presented in Table 4.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the Simponi treatment group than in the control group (p = 0.003). The radiographic effects observed at week 52 were maintained through week 104. Among patients remaining in the study and treated with Simponi, radiographic effects were similar from week 104 through week 256.

Table 4
Radiographic mean (SD) changes from baseline in total vdH-S score at week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Simponi 50 mg + MTX**
n[a]	**160**	**159**
Total Score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion Score		
Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.7 (2.8)	0.5 (2.1)
JSN Score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)**

[a] n reflects randomised patients
* p = 0.015
** p = 0.044

Physical function and health-related quality of life
Physical function and disability were assessed as a separate endpoint in GO-FORWARD and GO-AFTER using the disability index of the HAQ DI. In these studies, Simponi demonstrated clinically meaningful and statistically significant improvement in HAQ DI from baseline versus control at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement in HAQ DI was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement in HAQ DI was similar from week 104 through week 256.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with Simponi versus placebo at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement of the SF-36 physical component was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement of the SF-36 physical component was similar from week 104 through week 256. In GO-FORWARD and GO-AFTER, statistically significant improvements were observed in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F).

Adult psoriatic arthritis
The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months and had at least mild psoriatic disease. Patients with each sub-type of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). Previous treatment with an anti-TNF agent was not allowed. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg, or

Simponi 100 mg. Patients receiving placebo were switched to Simponi 50 mg after week 24. Patients entered an open label long-term extension at week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at week 14 and change from baseline in total PsA modified vdH-S score at week 24.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 104. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms
Key results for the 50 mg dose at weeks 14 and 24 are shown in Table 5 and described below.

Table 5
Key efficacy outcomes from GO-REVEAL

	Placebo	Simponi 50 mg*
n[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	**9%**	**51%**
Week 24	12%	52%
ACR 50		
Week 14	2%	30%
Week 24	4%	32%
ACR 70		
Week 14	1%	12%
Week 24	1%	19%
PASI[b] 75[c]		
Week 14	3%	40%
Week 24	1%	56%

* $p < 0.05$ for all comparisons;

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

[b] *Psoriasis Area and Severity Index*

[c] Based on the subset of patients with ≥ 3% BSA involvement at baseline, 79 patients (69.9%) in the placebo group and 109 (74.3%) in the Simponi 50 mg group.

Responses were observed at the first assessment (week 4) after the initial Simponi administration. Similar ACR 20 responses at week 14 were observed in patients with polyarticular arthritis with no rheumatoid nodules and asymmetric peripheral arthritis PsA subtypes. The number of patients with other PsA subtypes was too small to allow meaningful assessment. Responses observed in the Simponi treated groups were similar in patients receiving and not receiving concomitant MTX. Among 146 patients randomised to Simponi 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 ($p < 0.05$).

At week 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Simponi-treated patients. Simponi treatment resulted in significant improvement in physical function as assessed by HAQ DI, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36. Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 and HAQ DI

responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 and HAQ DI responses were similar from week 104 through week 256.

Radiographic response
Structural damage in both hands and feet was assessed radiographically by the change from baseline in the vdH-S score, modified for PsA by addition of hand distal interphalangeal (DIP) joints.

Simponi 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean ± SD score was 0.27 ± 1.3 in the placebo group compared with -0.16 ± 1.3 in the Simponi group; p = 0.011). Out of 146 patients who were randomised to Simponi 50 mg, 52 week X-ray data were available for 126 patients, of whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline. Among patients remaining in the study and treated with Simponi, similar rates of patients showed no progression from baseline from week 104 through week 256.

Adult axial spondyloarthritis
Adult ankylosing spondylitis
The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and a VAS for total back pain of ≥ 4, on a scale of 0 to 10 cm). Patients enrolled in this study had active disease despite current or previous NSAID or DMARD therapy and had not previously been treated with anti-TNF therapy. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg and Simponi 100 mg and were allowed to continue concomitant DMARD therapy (MTX, SSZ and/or HCQ). The primary endpoint was the percentage of patients achieving Ankylosing Spondylitis Assessment Study Group (ASAS) 20 response at week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

Key results for the 50 mg dose are shown in Table 6 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 24. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Table 6
Key efficacy outcomes from GO-RAISE

	Placebo	Simponi 50 mg*
n[a]	78	138
Responders, % of patients		
ASAS 20		
Week 14	**22%**	**59%**
Week 24	23%	56%
ASAS 40		
Week 14	15%	45%
Week 24	15%	44%
ASAS 5/6		
Week 14	8%	50%
Week 24	13%	49%

* $p \leq 0.001$ for all comparisons
[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

Among patients remaining in the study and treated with Simponi, the proportion of patients with an ASAS 20 and ASAS 40 response were similar from week 24 through week 256.

Statistically significant responses in BASDAI 50, 70 and 90 ($p \leq 0.017$) were also seen at weeks 14 and 24. Improvements in key measures of disease activity were observed at the first assessment

(week 4) after the initial Simponi administration and were maintained through week 24. Among patients remaining in the study and treated with Simponi, similar rates of change from baseline in BASDAI were observed from week 24 through week 256. Consistent efficacy was seen in patients regardless of use of DMARDs (MTX, sulfasalazine and/or hydroxychloroquine), HLA-B27 antigen status or baseline CRP levels as assessed by ASAS 20 responses at week 14.

Simponi treatment resulted in significant improvements in physical function as assessed by changes from baseline in BASFI at weeks 14 and 24. Health-related quality of life as measured by the physical component score of the SF-36 was also improved significantly at weeks 14 and 24. Among patients remaining in the study and treated with Simponi, improvements in physical function and health-related quality of life were similar from week 24 through week 256.

Adult non-radiographic axial spondyloarthritis

GO-AHEAD

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-AHEAD) in 197 adult patients with severe active nr-Axial SpA (defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS). Patients enrolled in this study had active disease (defined as a BASDAI ≥ 4 and a Visual Analogue Scale (VAS) for total back pain of ≥ 4, each on a scale of 0-10 cm) despite current or previous NSAID therapy and had not previously been treated with any biological agents including anti-TNF therapy. Patients were randomly assigned to placebo or Simponi 50 mg administered subcutaneously every 4 weeks. At week 16, patients entered an open label period in which all patients received Simponi 50 mg administered subcutaneously every 4 weeks through week 48 with efficacy assessments performed through week 52 and safety follow-up through week 60. Approximately 93% of patients who were receiving Simponi at the beginning of the open-label extension (week 16) remained on treatment through the end of the study (week 52). Analyses were performed on both the All Treated (AT, N = 197) and Objective Signs of Inflammation (OSI, N = 158, defined by elevated CRP and/or evidence of sacroiliitis on MRI at baseline) populations. Placebo-controlled efficacy data were collected and analysed through week 16. The primary endpoint was the proportion of patients achieving ASAS 20 response at week 16. Key results are shown in Table 7 and described below.

Table 7
Key efficacy outcomes from GO-AHEAD at week 16

Improvements in signs and symptoms				
	All treated population (AT)		Objective signs of inflammation population (OSI)	
	Placebo	Simponi 50 mg	Placebo	Simponi 50 mg
n[a]	100	97	80	78
Responders, % of patients				
ASAS 20	40%	71%**	38%	77%**
ASAS 40	23%	57%**	23%	60%**
ASAS 5/6	23%	54%**	23%	63%**
ASAS Partial Remission	18%	33%*	19%	35%*
ASDAS-C [b] < 1.3	13%	33%*	16%	35%*
BASDAI 50	30%	58%**	29%	59%**
Inhibition of inflammation in sacroiliac (SI) joints as measured by MRI				
	Placebo	Simponi 50 mg	Placebo	Simponi 50 mg
n[c]	87	74	69	61
Mean change in SPARCC[d] MRI sacroiliac joint score	-0.9	-5.3**	-1.2	-6.4**

[a] n reflects randomised and treated patients

[b] Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (AT-Placebo, N = 90; AT-Simponi 50 mg, N = 88; OSI-Placebo, N = 71; OSI-Simponi 50 mg, N = 71)

[c] n reflects number of patients with baseline and week 16 MRI data

[d] SPARCC (Spondyloarthritis Research Consortium of Canada)

** $p < 0.0001$ for Simponi *vs* placebo comparisons

* $p < 0.05$ for Simponi *vs* placebo comparisons

Statistically significant improvements in signs and symptoms of severe active nr-Axial SpA were demonstrated in patients treated with Simponi 50 mg compared to placebo at week 16 (Table 6). Improvements were observed at the first assessment (week 4) after the initial Simponi administration. SPARCC score as measured by MRI showed statistically significant reductions in SI joint inflammation at week 16 in patients treated with Simponi 50 mg compared to placebo (Table 6). Pain as assessed by the Total Back Pain and Nocturnal Back Pain VAS, and disease activity as measured by ASDAS-C also showed statistically significant improvement from baseline to week 16 in patients treated with Simponi 50 mg compared to placebo ($p < 0.0001$).

Statistically significant improvements in spinal mobility as assessed by BASMI (Bath Ankylosing Spondylitis Metrology Index) and in physical function as assessed by the BASFI were demonstrated in Simponi 50 mg-treated patients as compared to placebo-treated patients ($p < 0.0001$). Patients treated with Simponi experienced significantly more improvements in health-related quality of life as assessed by ASQoL, EQ-5D, and physical and mental components of SF-36, and experienced significantly more improvements in productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI questionnaire than patients receiving placebo.

For all of the endpoints described above, statistically significant results were also demonstrated in the OSI population at week 16.

In both the AT and OSI populations, the improvements in signs and symptoms, spinal mobility, physical function, quality of life, and productivity observed at week 16 among patients treated with Simponi 50 mg continued in those remaining in the study at week 52.

GO-BACK

The efficacy and safety of continued golimumab treatment (full or reduced dosing frequency) compared with treatment withdrawal was assessed in adult patients (18-45 years of age) with active nr-axSpA who demonstrated sustained remission during 10 months of monthly treatment with open-label Simponi (GO-BACK). Eligible patients (who achieved a clinical response by Month 4 and an inactive disease status (ASDAS < 1.3) at both Months 7 and 10) entering the double-blind withdrawal phase were randomised to continued monthly treatment with Simponi (full-treatment regimen, N = 63), every 2-month treatment with Simponi (reduced treatment regimen, N = 63) or monthly placebo treatment (treatment withdrawal, N = 62) for up to approximately 12 months.

The primary efficacy endpoint was the proportion of patients without a flare of disease activity. Patients who experienced a flare, i.e., had an ASDAS collected at 2 consecutive assessments that both showed either an absolute score of ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (end of open-label period), reinitiated monthly Simponi in an open-label retreatment phase to characterise clinical response.

Clinical response after double-blind treatment withdrawal
Among the 188 patients with inactive disease who received at least one dose of double-blind treatment, a significantly ($p < 0.001$) greater proportion of patients did not experience a disease flare when continuing Simponi with either the full-treatment (84.1%), or reduced treatment (68.3%) regimens compared with treatment withdrawal (33.9%) (Table 8).

Table 8
Analysis of the proportion of participants without a flare[a]
Full analysis set population (Period 2 – Double-blind)

Treatment	n/N	%	Difference in % vs Placebo	
			Estimate (95% CI)[b]	p-Value[b]
GLM SC QMT	53/63	84.1	50.2 (34.1, 63.6)	< 0.001
GLM SC Q2MT	43/63	68.3	34.4 (17.0, 49.7)	< 0.001
Placebo	21/62	33.9		

Full Analysis Set includes all randomised participants who attained inactive disease in period 1 and received at least one dose of blinded study treatment.

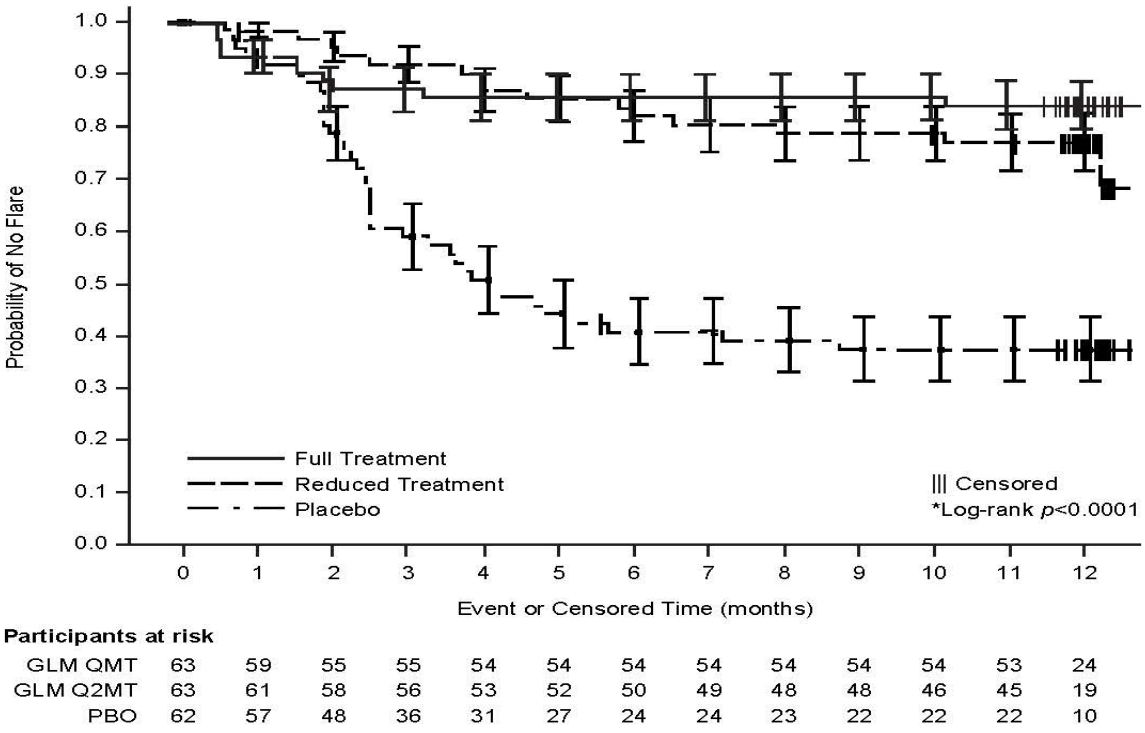
[a] Defined as ASDAS at 2 consecutive visits that both show either absolute score ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23).

[b] Type I error rate over the multiple treatment comparisons (GLM SC QMT vs Placebo and GLM SC Q2MT vs Placebo) was controlled using a sequential (step-down) testing procedure. Derived based on the stratified Miettinen and Nurminen method with CRP level (> 6 mg/L or ≤ 6 mg/L) as stratification factor.

Participants who discontinued period 2 prematurely and prior to a 'flare' will be counted as having a 'flare'.
N = Total number of participants; n = number of participants without a flare; GLM = golimumab; SC = subcutaneous, QMT = monthly dosing; Q2MT = every other month dosing.

The difference in time-to-first flare between the treatment withdrawal group and either of the Simponi Treatment groups is shown in Figure 1 (log-rank p < 0.0001 for each comparison). In the placebo group, flares started approximately 2 months after Simponi was withdrawn, with the majority of flares occurring within 4 months of treatment withdrawal (Figure 1).

Figure 1: Kaplan-Meier Analysis of Time-to-First Flare



*Endpoint not adjusted for multiplicity. Stratified by CRP level (> 6 mg/L or ≤ 6 mg/L). Flare was defined as an ASDAS at 2 consecutive visits that both showed either an absolute score of ≥ 2.1 or a post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23). Participants who did not flare were censored at the time of discontinuation or Month 13 of Period 2 double-blind treatment. Start of Period 2 represents Day 1 of the Kaplan-Meier analysis for the full analysis set.

Clinical response to retreatment for a disease flare
Clinical response was defined as a BASDAI improvement of ≥ 2 or ≥ 50% relative to the mean of the 2 consecutive BASDAI scores ascribed to the disease flare. Of the 53 participants in the reduced dosing or treatment withdrawal regimens who had a confirmed disease flare, 51 (96.2%) attained a

clinical response to Simponi within the first 3 months of retreatment, although fewer patients (71.7%) were able to sustain it for all 3 months.

Adult ulcerative colitis
The efficacy of Simponi was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients.

The induction study (PURSUIT-Induction) evaluated patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) who had an inadequate response to or failed to tolerate conventional therapies, or were corticosteroid dependent. In the dose confirming portion of the study, 761 patients were randomised to receive either 400 mg Simponi SC at week 0 and 200 mg at week 2, 200 mg Simponi SC at week 0 and 100 mg at week 2, or placebo SC at weeks 0 and 2. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. The efficacy of Simponi through week 6 was assessed in this study.

The results of the maintenance study (PURSUIT-Maintenance) were based on evaluation of 456 patients who achieved clinical response from previous induction with Simponi. Patients were randomised to receive Simponi 50 mg, Simponi 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, and/or immunomodulatory agents were permitted. Corticosteroids were to be tapered at the start of the maintenance study. The efficacy of Simponi through week 54 was assessed in this study. Patients who completed the maintenance study through week 54 continued treatment in a study extension, with efficacy evaluated through week 216. Efficacy evaluation in the study extension was based on changes in corticosteroid use, Physician's Global Assessment (PGA) of disease activity, and improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire (IBDQ).

Table 9
Key efficacy outcomes from PURSUIT - Induction and PURSUIT - Maintenance

PURSUIT-Induction			
	Placebo N = 251	**Simponi 200/100 mg** N = 253	
Percentage of patients			
Patients in clinical response at week 6[a]	30%	51%**	
Patients in clinical remission at week 6[b]	6%	18%**	
Patients with mucosal healing at week 6[c]	29%	42%*	
PURSUIT-Maintenance			
	Placebo[d] N = 154	**Simponi 50 mg** N = 151	**Simponi 100 mg** N = 151
Percentage of patients			
Maintenance of response (Patients in clinical response through week 54)[e]	31%	47%*	50%**
Sustained remission (Patients in clinical remission at both week 30 and week 54)[f]	16%	23%[g]	28%*

N = number of patients
** $p \leq 0.001$
* $p \leq 0.01$
[a] defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.
[b] Defined as a Mayo score ≤ 2 points, with no individual subscore > 1
[c] Defined as 0 or 1 on the endoscopy subscore of the Mayo score.
[d] Simponi induction only.
[e] Patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). Therefore, a patient who maintained response was in a state of continuous clinical response at each evaluation through week 54.
[f] A patient had to be in remission at both weeks 30 and 54 (without demonstrating a loss of response at any time point through week 54) to achieve durable remission.
[g] In patients weighing less than 80 kg, a greater proportion of patients who received 50 mg maintenance therapy showed sustained clinical remission compared with those who received placebo.

More Simponi-treated patients demonstrated sustained mucosal healing (patients with mucosal healing at both week 30 and week 54) in the 50 mg group (42%, nominal $p < 0.05$) and 100 mg group (42%, $p < 0.005$) compared with patients in the placebo group (27%).

Among the 54% of patients (247/456) who were receiving concomitant corticosteroids at the start of PURSUIT-Maintenance, the proportion of patients who maintained clinical response through week 54 and were not receiving concomitant corticosteroids at week 54 was greater in the 50 mg group (38%, 30/78) and 100 mg group (30%, 25/82) compared with the placebo group (21%, 18/87). The proportion of patients who eliminated corticosteroids by week 54 was greater in the 50 mg group (41%, 32/78) and 100 mg group (33%, 27/82) compared with the placebo group (22%, 19/87). Among patients who entered the study extension, the proportion of subjects who remained corticosteroid free was generally maintained through week 216.

Patients who did not achieve clinical response at week 6 in the PURSUIT-Induction studies were dosed Simponi 100 mg every 4 weeks in the PURSUIT-Maintenance study. At week 14, 28% of these patients achieved response defined by partial Mayo score (decreased by ≥ 3 points compared with start of induction). At week 54, the clinical outcomes observed in these patients were similar to the clinical outcomes reported for the patients achieving clinical response at week 6.

At week 6, Simponi significantly improved quality of life as measured by change from baseline in a disease specific measure, IBDQ (inflammatory bowel disease questionnaire). Among patients who received Simponi maintenance treatment, the improvement in quality of life as measured by IBDQ was maintained through week 54.

Approximately 63% of patients who were receiving Simponi at the beginning of the study extension (week 56), remained on treatment through the end of the study (last golimumab administration at week 212).

Paediatric population

Paediatric polyarticular juvenile idiopathic arthritis
The safety and efficacy of Simponi was evaluated in a randomised, double-blind, placebo-controlled, withdrawal study (GO-KIDS) in 173 children (2 to 17 years of age) with active pJIA with at least 5 active joints and an inadequate response to MTX. Children with polyarticular course JIA (rheumatoid factor positive or negative polyarthritis, extended oligoarthritis, juvenile psoriatic arthritis or systemic JIA with no current systemic symptoms) were included in the study. The baseline median number of active joints was 12, and median CRP was 0.17 mg/dL.

Part 1 of the study consisted of a 16-week open-label phase in which 173 enrolled children received Simponi 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks and MTX. The 154 children who achieved an ACR Ped 30 response at week 16 entered Part 2 of the study, the randomised withdrawal phase, and received Simponi 30 mg/m^2 (maximum 50 mg) + MTX or placebo + MTX every 4 weeks.

After disease flare, children received Simponi 30 mg/m^2 (maximum 50 mg) + MTX. At week 48, children entered a long-term extension.

Children in this study demonstrated ACR Ped 30, 50, 70, and 90 responses from week 4.

At week 16, 87% of children were ACR Ped 30 responders, and 79%, 66%, and 36% of children were ACR Ped 50, ACR Ped 70, and ACR Ped 90 responders, respectively. At week 16, 34% of children had inactive disease defined as having the presence of all of the following: no joints with active arthritis; no fever, rash, serositis, splenomegaly, hepatomegaly, or generalised lymphadenopathy attributable to JIA; no active uveitis; normal ESR (< 20 mm/hour) or CRP (< 1.0 mg/dL); physician global assessment of disease activity (≤ 5 mm on the VAS); duration of morning stiffness < 15 minutes.

At week 16, all ACR Ped components demonstrated clinically relevant improvement from baseline (see Table 10).

Table 10
Improvements from baseline in ACR Ped components at week 16[a]

	Median percent improvement
	Simponi 30 mg/m^2 n[b] = 173
Physicians global assessment of disease (VAS[c] 0-10 cm)	88%
Subject/parent global assessment of overall well-being (VAS 0-10 cm)	67%
Number of active joints	92%
Number of joints with limited range of motion	80%
Physical function by CHAQ[d]	50%
ESR (mm/h)[e]	33%

[a] baseline = week 0

[b] "n" reflects enrolled patients

[c] VAS: Visual Analogue Scale

[d] CHAQ: Child Health Assessment Questionnaire

[e] ESR (mm/h): erythrocyte sedimentation rate (millimetres per hour)

The primary endpoint, the proportion of children who were ACR Ped 30 responders at week 16 and who did not experience a flare between week 16 and week 48, was not achieved. The majority of children did not experience a flare between week 16 and week 48 (59% in the Simponi + MTX and 53% in the placebo + MTX groups, respectively; p = 0.41).

Pre-specified subgroup analyses of the primary endpoint by baseline CRP (≥ 1 mg/dL vs < 1 mg/dL) demonstrated higher flare rates in placebo + MTX vs Simponi + MTX treated subjects among subjects with baseline CRP ≥ 1 mg/dL (87% vs 40% p = 0.0068).

At week 48, 53% and 55% of children in the Simponi + MTX group and placebo + MTX group, respectively, were ACR Ped 30 responders, and 40% and 28% of children in the Simponi + MTX group and placebo + MTX group, respectively, achieved inactive disease.

Paediatric ulcerative colitis
The safety and efficacy of Simponi was evaluated in a Phase III multi-centre, open-label, study (PURSUIT 2) designed to enroll children 2 to 17 years of age with moderately to severely active UC defined as a baseline full Mayo score of 6 through 12, inclusive, with an endoscopy subscore of ≥ 2. Children with prior exposure to anti-TNF-α agents were ineligible for participation. The majority of the 69 participants (97.1%) were receiving UC-related medications (corticosteroids, immunomodulators, and/or 5-ASA); 52.2% of participants were receiving corticosteroids, and 88.4% were receiving oral 5-ASA.The mean age of participants was 13.4 years (range 4 to 17). 53.6% (37) of participants were female. The mean weight was 52.4 kg (range 16 to 107). Baseline disease

characteristics for the overall golimumab population were representative of paediatric patients with moderately to severely active UC.

In the Induction Phase (week 0 to week 6), children received body weight-based golimumab SC, at weeks 0 and 2. Children with body weight ≥ 45 kg received fixed induction doses of 200 mg SC at week 0 and 100 mg at week 2. Children with body weight < 45 kg received body-surface area-adjusted induction doses of 120 mg/m^2 SC (up to a maximum of 200 mg) at week 0 and 60 mg/m^2 SC (up to a maximum of 100 mg) at week 2. At week 6, children were evaluated for efficacy and safety.

In the Maintenance Phase (week 6 through week 54), children in clinical response to golimumab (a decrease from baseline in the full Mayo score of ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1 using the local read for the endoscopy subscore) continued to receive SC golimumab 100 mg (children weighing ≥ 45 kg) or 60 mg/m^2 (children weighing < 45 kg) every 4 weeks through week 50. For children with no clinical response at week 6, additional doses at week 6 and week 10 could have been given, followed by a response assessment at week 14 to determine if the children continued with golimumab every 4 weeks through week 50. Of the 41 children who entered the maintenance phase, 39 children remained in the study at week 54 (had a full Mayo score efficacy determination).

The primary endpoint of clinical remission as measured by the Mayo score was defined as a Mayo score ≤ 2 points, with no individual subscore > 1 (based on Mayo endoscopy subscore assigned by the local endoscopist). Overall, 22 (31.9%) of children showed clinical remission at week 6. At week 54, 31.7% of week 6 clinical responders were in clinical remission.

Table 11
Key efficacy outcomes from PURSUIT 2 – Induction and PURSUIT 2 - Maintenance

PURSUIT 2 – Induction	
Primary Endpoint	**Simponi N=69**
Subjects in clinical remission as assessed by the Mayo score at week 6 [a]	22 (31.9%)
Major Secondary Endpoints	
Subjects in clinical response at week 6[b]	39 (56.5%)
Subjects with endoscopic healing at week 6[c]	28 (40.6%)
PURSUIT 2 – Maintenance	
Major Secondary Endpoints	**Simponi N=41**
Subjects in clinical remission at week 54 as assessed by the Mayo score[a,e]	13 (31.7%)
Subjects with endoscopic healing at week 54[c]	15 (36.6%)
Subjects in clinical remission at week 54 as assessed by the Mayo score, for participants who are in clinical remission at Week 6[a,d,e]	12 (54.5%)

N = number of patients

[a] Clinical remission is defined as a Mayo score ≤2 points, with no individual subscore >1.

[b] Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

[c] Endoscopic healing is defined as an endoscopy subscore of 0 or 1 based on local endoscopy.

[d] Denominator is subjects who were in clinical remission at Week 6.

[e] Subjects who had a missing endoscopy score at Week 54 were considered not to be in clinical remission.

Immunogenicity

Across the Phase III RA, PsA and AS studies through week 52, antibodies to golimumab were detected by the enzyme immunoassay (EIA) method in 5% (105/2062) of golimumab treated patients and, where tested, nearly all antibodies were neutralising *in vitro*. Similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of

patients with antibodies to golimumab than patients receiving golimumab without MTX (approximately 3% [41/1235] versus 8% [64/827], respectively).

In nr-Axial SpA, antibodies to golimumab were detected in 7% (14/193) of golimumab treated patients through week 52 by the EIA method.

In the Phase II and III UC studies through week 54, antibodies to golimumab were detected by the EIA method in 3% (26/946) of golimumab treated patients. Sixty-eight percent (21/31) of antibody-positive patients had neutralising antibodies *in vitro*. Treatment with concomitant immunomodulators (azathioprine, 6-mercaptopurine and MTX) resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without immunomodulators (1% (4/308) versus 3% (22/638), respectively). Of patients that continued in the study extension and had evaluable samples through week 228, antibodies to golimumab were detected in 4% (23/604) of golimumab treated patients. Eighty-two percent (18/22) of antibody-positive patients had neutralising antibodies *in vitro*.

A drug-tolerant EIA method was used in the pJIA study for the detection of antibodies to golimumab. Due to the higher sensitivity and the improved drug tolerance, a higher incidence of antibodies to golimumab was expected to be detected with the drug-tolerant EIA method compared to the EIA method. In the Phase III pJIA study through week 48, antibodies to golimumab were detected by the drug-tolerant EIA method in 40% (69/172) of golimumab treated children of which a majority had a titre lower than 1:1000. An effect on serum golimumab concentrations was seen at titres of > 1:100 while an effect on efficacy was not seen until titres of > 1:1000, though the numbers of children with titres of > 1:1000 were low (N = 8). Among the children who tested positive for antibodies to golimumab, 39% (25/65) had neutralising antibodies. The higher incidence of antibodies with the drug-tolerant EIA method, because they were mainly low titre antibodies, did not have an apparent impact on drug levels, efficacy and safety and therefore does not represent any new safety signal.

The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.8). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

Because immunogenicity analyses are product- and assay-specific, comparison of antibody rates with those from other products is not appropriate.

In the Phase III paediatric UC trial, 22% (15/69) of Simponi-treated patients were positive for antibodies to golimumab through the final safety visit using the drug-tolerant EIA method. Most patients with antibodies had low titres. The incidence of antibodies to golimumab was comparable between paediatric and adult patients with UC. UC patients who developed antibodies to golimumab, generally had lower trough steady-state serum concentrations of golimumab.

5.2 Pharmacokinetic properties

Absorption
Following a single subcutaneous administration of golimumab to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A subcutaneous injection of 50 mg golimumab to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/mL.

Following a single subcutaneous injection of 100 mg, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since golimumab exhibited approximately dose proportional PK following a subcutaneous administration, the absolute bioavailability of a golimumab 50 mg or 200 mg dose is expected to be similar.

Distribution
Following a single IV administration, the mean volume of distribution was 115 ± 19 mL/kg.

Elimination
The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg. Terminal half-life value was estimated to be approximately 12 ± 3 days in healthy subjects and similar values were observed in patients with RA, PsA, AS, or UC.

When 50 mg golimumab was administered subcutaneously to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by week 12. With concomitant use of MTX, treatment with 50 mg golimumab subcutaneously every 4 weeks resulted in a mean (± standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 μg/mL in patients with active PsA and approximately 0.8 ± 0.4 μg/mL in patients with AS. Steady-state trough mean serum golimumab concentrations in patients with nr-Axial SpA were similar to those observed in patients with AS following subcutaneous administration of 50 mg golimumab every 4 weeks.

Patients with RA, PsA or AS who did not receive concomitant MTX had approximately 30% lower steady-state trough concentrations of golimumab than those who received golimumab with MTX. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. However, population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

Following induction doses of 200 mg and 100 mg golimumab at week 0 and 2, respectively, and maintenance doses of 50 mg or 100 mg golimumab subcutaneously every 4 weeks thereafter to patients with UC, serum golimumab concentrations reached steady state approximately 14 weeks after the start of therapy. Treatment with 50 mg or 100 mg golimumab subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 0.9 ± 0.5 μg/mL and 1.8 ± 1.1 μg/mL, respectively.

In UC patients treated with 50 mg or 100 mg golimumab subcutaneously every 4 weeks, concomitant use of immunomodulators did not have a substantial effect on steady-state trough levels of golimumab.

Patients who developed antibodies to golimumab generally had low trough steady-state serum concentrations of golimumab (see section 5.1).

Linearity
Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose. Following a single SC dose in healthy subjects, approximately dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg.

Effect of weight on pharmacokinetics
There was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

Paediatric population

Polyarticular juvenile idiopathic arthritis
The pharmacokinetics of golimumab were determined in 173 children with pJIA with an age range from 2 to 17 years of age. In the pJIA study, children who received golimumab 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks, had median steady-state trough golimumab concentrations which were similar across different age groups, and which were also similar to or slightly higher than those seen in adult RA patients who received 50 mg golimumab every 4 weeks.

Population pharmacokinetic/pharmacodynamic modelling and simulation in children with pJIA confirmed the relationship between golimumab serum exposures and clinical efficacy and supports

that the dosing regimen of golimumab 50 mg every 4 weeks in children with pJIA of at least 40 kg achieves similar exposures to those shown to be efficacious in adults.

Ulcerative colitis
The pharmacokinetics of golimumab were similar between paediatric and adult patients with ulcerative colitis. Population pharmacokinetics confirmed that the recommended dosing regimen for Simponi resulted in similar or slightly higher serum golimumab exposure in paediatric subjects as compared to adults across the body weight range.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

No mutagenicity studies, animal fertility studies nor long-term carcinogenic studies have been conducted with golimumab.

In a fertility and general reproductive function study in mouse, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, the number of pregnant mice was reduced. It is not known whether this finding was due to effects on the males and/or the females. In a developmental toxicity study conducted in mice following administration of the same analogous antibody, and in cynomolgus monkeys using golimumab, there was no indication of maternal toxicity, embryotoxicity or teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect it from light.
Simponi may be stored at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 30 days from the date removed from the refrigerator).

Once Simponi has been stored at room temperature, it should not be returned to refrigerated storage. Simponi must be discarded if not used within the 30 days of room temperature storage.

6.5 Nature and contents of container

Simponi 50 mg solution for injection in pre-filled syringe
0.5 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex). Simponi is available in packs containing 1 pre-filled syringe and multipacks containing 3 (3 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Simponi is supplied in a single use pre-filled syringe. Each pack is provided with instructions for use that fully describe the use of the syringe. After removing the pre-filled syringe from the refrigerator it should be allowed to reach room temperature by waiting for 30 minutes, before injecting Simponi. The syringe should not be shaken.

The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for solutions containing protein. Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

Comprehensive instructions for the preparation and administration of Simponi in a pre-filled syringe are given in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/003 1 pre-filled syringe
EU/1/09/546/004 3 pre-filled syringes

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 October 2009
Date of latest renewal: 19 June 2014

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

Simponi 50 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 0.5 mL pre-filled pen contains 50 mg of golimumab*.

* Human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology.

Excipients with known effect
Each pre-filled pen contains 20.5 mg sorbitol (E420) per 50 mg dose.

Each pre-filled pen contains 0.075 mg of polysorbate 80 (E433) per 50 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled pen (SmartJect)

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)
Simponi, in combination with methotrexate (MTX), is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

Simponi, in combination with MTX, 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
Polyarticular juvenile idiopathic arthritis (pJIA)
Simponi in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Psoriatic arthritis (PsA)
Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Simponi has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Axial spondyloarthritis
Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)
Simponi is indicated for the treatment of adults with severe, active 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, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)
Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

4.2 Posology and method of administration

Treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis. Patients treated with Simponi should be given the Patient Card.

Posology

Rheumatoid arthritis
Simponi 50 mg given once a month, on the same date each month.
Simponi should be given concomitantly with MTX.

Psoriatic arthritis, ankylosing spondylitis, or non-radiographic axial spondyloarthritis
Simponi 50 mg given once a month, on the same date each month.

For all of the above indications, available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Patients with body weight greater than 100 kg
For all of the above indications, in patients with RA, PsA, AS, or nr-Axial SpA with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse reactions with the 100 mg dose compared with the 50 mg dose (see section 4.8). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

Adult ulcerative colitis
Patients with body weight less than 80 kg
Simponi given as an initial dose of 200 mg, followed by 100 mg at week 2. Patients who have an adequate response should receive 50 mg at week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter (see section 5.1).

Patients with body weight greater than or equal to 80 kg
Simponi given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter (see section 5.1).

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Missed dose
If a patient forgets to inject Simponi on the planned date, the forgotten dose should be injected as soon as the patient remembers. Patients should be instructed not to inject a double dose to make up for the forgotten dose.

The next dose should be administered based on the following guidance:
- if the dose is less than 2 weeks late, the patient should inject the forgotten dose and stay on the original schedule.
- if the dose is more than 2 weeks late, the patient should inject the forgotten dose and a new schedule should be established from the date of this injection.

Special populations
Elderly (≥ 65 years)
No dose adjustment is required in the elderly.

Renal and hepatic impairment
Simponi has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of Simponi in patients aged less than 18 for indications other than pJIA and pUC have not been established. No data are available. There is no relevant use of Simponi in children aged less than 2 years in pJIA or pUC. Simponi 50 mg pre-filled pen has not been studied in pUC and is not recommended for use in this paediatric population. See section 4.2 of the 50 mg or 100 mg pre-filled syringe or of the 45 mg/0.45 mL pre-filled pen SmPC for posology and method of administration in pUC patients (from 2 years of age and above 15 kg).

Polyarticular juvenile idiopathic arthritis
Simponi 50 mg administered once a month, on the same date each month, for children with a body weight of at least 40 kg. A 45 mg/0.45 mL pre-filled pen is available for administration to children with polyarticular juvenile idiopathic arthritis weighing less than 40 kg.

Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in children who show no evidence of therapeutic benefit within this time period.

Method of administration
Simponi is for subcutaneous use. After proper training in subcutaneous injection technique, patients may self-inject if their physician determines that this is appropriate, with medical follow-up as necessary. Patients should be instructed to inject the full amount of Simponi according to the comprehensive instructions for use provided in the package leaflet. If multiple injections are required, the injections should be administered at different sites on the body. Each pre-filled pen is for single use in a single patient, and should be discarded immediately after use.

For administration instructions, see section 6.6.

4.3 Contraindications

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

Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate or severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Patients must be monitored closely for infections including tuberculosis before, during and after treatment with golimumab. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. Further treatment with golimumab must not be given if a patient develops a serious infection or sepsis (see section 4.3).

Golimumab should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of golimumab in patients with a chronic infection or a history of recurrent infection. Patients should be advised of, and avoid exposure to, potential risk factors for infection as appropriate.

Patients taking TNF-blockers are more susceptible to serious infections.
Bacterial (including sepsis and pneumonia), mycobacterial (including TB), invasive fungal and opportunistic infections, including fatalities, have been reported in patients receiving golimumab. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with golimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of golimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of golimumab treatment should be carefully considered before initiation of golimumab therapy. In at-risk patients treated with golimumab, an invasive fungal infection should be suspected if they develop a serious systemic illness. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections, if feasible.

Tuberculosis
There have been reports of tuberculosis in patients receiving golimumab. It should be noted that in the majority of these reports, tuberculosis was extrapulmonary presenting as either local or disseminated disease.

Before starting treatment with golimumab, 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 or blood 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, golimumab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of golimumab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of golimumab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of golimumab. Use of anti-tuberculosis therapy should also be considered before the initiation of golimumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Cases of active tuberculosis have occurred in patients treated with golimumab during and after treatment for latent tuberculosis. Patients receiving golimumab should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

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 golimumab treatment.

Hepatitis B virus reactivation
Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including golimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with golimumab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with golimumab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, golimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Malignancies and lymphoproliferative disorders
The potential role of TNF-blocking therapy in the development of malignancies is not known. Based on the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

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

Lymphoma and leukaemia
In the controlled portions of clinical trials of all the TNF-blocking agents including golimumab, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the Simponi Phase IIb and Phase III clinical trials in RA, PsA and AS, the incidence of lymphoma in golimumab-treated patients was higher than expected in the general population. Cases of leukaemia have been reported in patients treated with golimumab. 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.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with other TNF-blocking agents (see section 4.8). This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of cases have occurred in adolescent and young adult males with nearly all on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) for inflammatory bowel disease. The potential risk with the combination of AZA or 6-MP and golimumab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Malignancies other than lymphoma
In the controlled portions of the Simponi Phase IIb and Phase III clinical trials in RA, PsA, AS, and UC, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups.

Colon dysplasia/carcinoma
It is not known if golimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with golimumab, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

In an exploratory clinical trial evaluating the use of golimumab in patients with severe persistent asthma, more malignancies were reported in patients treated with golimumab compared with control patients (see section 4.8). The significance of this finding is unknown.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with an increased risk of malignancy due to heavy smoking.

Skin cancers
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents, including golimumab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

Congestive heart failure (CHF)
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including golimumab. Some cases had a fatal outcome. In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to CHF have been observed. Golimumab has not been studied in patients with CHF. Golimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and golimumab must be discontinued in patients who develop new or worsening symptoms of heart failure (see section 4.3).

Neurological events
Use of TNF-blocking agents, including golimumab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy. Discontinuation of golimumab should be considered if these disorders develop (see section 4.8).

Surgery
There is limited safety experience of golimumab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on golimumab should be closely monitored for infections, and appropriate actions should be taken.

Immunosuppression
The possibility exists for TNF-blocking agents, including golimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Autoimmune processes
The relative deficiency of TNF_{α} caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with golimumab and is positive for antibodies against double-stranded DNA, treatment with golimumab should be discontinued (see section 4.8).

Haematologic reactions
There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anaemia, and thrombocytopenia in patients receiving TNF-blockers, including golimumab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of golimumab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent administration of TNF-antagonists and anakinra
Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. The combination of golimumab and anakinra is not recommended.

Concurrent administration of TNF-antagonists and abatacept
In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of golimumab and abatacept is not recommended.

Concurrent administration with other biological therapeutics
There is insufficient information regarding the concomitant use of golimumab with other biological therapeutics used to treat the same conditions as golimumab. The concomitant use of golimumab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs
Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Vaccinations/therapeutic infectious agents
Patients treated with golimumab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6). In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g. BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with golimumab.

Allergic reactions
In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following golimumab administration. Some of these reactions occurred after the first administration of golimumab. If an anaphylactic reaction or other serious allergic reactions occur, administration of golimumab should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity
The needle cover on the pre-filled pen or the pre-filled syringe is manufactured from dry natural rubber containing latex, and may cause allergic reactions in individuals sensitive to latex.

Special populations

Elderly (≥ 65 years)
In the Phase III studies in RA, PsA, AS, and UC, no overall differences in adverse events (AEs), serious adverse events (SAEs), and serious infections in patients age 65 or older who received golimumab 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. There were no patients age 45 and over in the nr-Axial SpA study.

Renal and hepatic impairment
Specific studies of golimumab have not been conducted in patients with renal or hepatic impairment. Golimumab should be used with caution in subjects with impaired hepatic function (see section 4.2).

Paediatrics
Vaccinations
If possible, it is recommended that prior to initiating golimumab therapy, paediatric patients be brought up to date with all immunisations in agreement with current immunisation guidelines (see Vaccinations/therapeutic infectious agents above).

Excipients with known effect
Sorbitol
Simponi contains sorbitol (E420). In patients with rare hereditary problems of fructose intolerance, the additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account (see section 2).

Polysorbate 80
Simponi contains 0.075 mg of polysorbate 80 (E433) in each pre-filled pen. Polysorbates may cause allergic reactions (see section 2).

Potential for medication errors
Simponi is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in the posology (see section 4.2). Care should be taken to provide the right strength to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with other biological therapeutics
The combination of golimumab with other biological therapeutics used to treat the same conditions as golimumab, including anakinra and abatacept is not recommended (see section 4.4).

Live vaccines/therapeutic infectious agents
Live vaccines should not be given concurrently with golimumab (see sections 4.4 and 4.6).

Therapeutic infectious agents should not be given concurrently with golimumab (see section 4.4).

Methotrexate
Although concomitant use of MTX results in higher steady-state trough concentrations of golimumab in patients with RA, PsA or AS, the data do not suggest the need for dose adjustment of either golimumab or MTX (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last golimumab treatment.

Pregnancy
There is a moderate amount (approximately 400) of prospectively collected pregnancies exposed to golimumab resulting in live birth with known outcomes, including 220 pregnancies exposed during the first trimester. In a population-based study from Northern Europe including 131 pregnancies (and 134 infants), there were 6/134 (4.5%) events of major congenital anomalies following *in utero* exposure to Simponi vs 599/10,823 (5.5%) events for non-biologic systemic therapy compared to 4.6% in the general population of the study. Confounder-adjusted odds ratios were OR 0.79 (95% CI 0.35-1.81) for Simponi vs. non-biologic systemic therapy and OR 0.95 (95% CI 0.42-2.16) for Simponi vs. the general population, respectively.

Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The available clinical experience is limited. Golimumab should only be used during pregnancy if clearly needed.

Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see sections 4.4 and 4.5).

Breast-feeding
It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Golimumab was shown to pass over to breast milk in monkeys, and because human immunoglobulins are excreted in milk, women must not breast feed during and for at least 6 months after golimumab treatment.

Fertility
No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, showed no relevant effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Simponi has minor influence on the ability to drive and use machines. Dizziness may however occur following administration of Simponi (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In the controlled period of the pivotal trials in RA, PsA, AS, nr-Axial SpA, and UC, upper respiratory tract infection was the most common adverse reaction (AR) reported in 12.6% of golimumab-treated patients compared with 11.0% of control patients. The most serious ARs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome), haematologic reactions, serious systemic hypersensitivity (including anaphylactic reaction), vasculitis, lymphoma and leukaemia (see section 4.4).

Tabulated list of adverse reactions

ARs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed in Table 1. Within the designated system organ classes, the ARs are listed under headings of frequency and using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1
Tabulated list of ARs

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)
Common:	Bacterial infections (such as cellulitis), lower respiratory tract infection (such as pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess
Uncommon:	Sepsis including septic shock, pyelonephritis
Rare:	Tuberculosis, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), hepatitis B reactivation, bacterial arthritis, infective bursitis
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia, melanoma, Merkel cell carcinoma
Not known:	Hepatosplenic T-cell lymphoma*, Kaposi's sarcoma
Blood and lymphatic system disorders	
Common:	Leukopenia (including neutropenia), anaemia
Uncommon:	Thrombocytopenia, pancytopenia
Rare:	Aplastic anaemia, agranulocytosis
Immune system disorders	
Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis

Endocrine disorders		
	Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders		
	Uncommon:	Blood glucose increased, lipids increased
Psychiatric disorders		
	Common:	Depression, insomnia
Nervous system disorders		
	Common:	Dizziness, headache, paraesthesia
	Uncommon:	Balance disorders
	Rare:	Demyelinating disorders (central and peripheral), dysgeusia
Eye disorders		
	Uncommon:	Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritus and irritation)
Cardiac disorders		
	Uncommon:	Arrhythmia, ischaemic coronary artery disorders
	Rare:	Congestive heart failure (new onset or worsening)
Vascular disorders		
	Common:	Hypertension
	Uncommon:	Thrombosis (such as deep venous and aortic), flushing
	Rare:	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders		
	Common:	Asthma and related symptoms (such as wheezing and bronchial hyperactivity)
	Uncommon:	Interstitial lung disease
Gastrointestinal disorders		
	Common:	Dyspepsia, gastrointestinal and abdominal pain, nausea, gastrointestinal inflammatory disorders (such as gastritis and colitis), stomatitis
	Uncommon:	Constipation, gastro-oesophageal reflux disease
Hepatobiliary disorders		
	Common:	Alanine aminotransferase increased, aspartate aminotransferase increased
	Uncommon:	Cholelithiasis, hepatic disorders
Skin and subcutaneous tissue disorders		
	Common:	Pruritus, rash, alopecia, dermatitis
	Uncommon:	Bullous skin reactions, psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria
	Rare:	Lichenoid reactions, skin exfoliation, vasculitis (cutaneous)
	Not known:	Worsening of symptoms of dermatomyositis
Musculoskeletal and connective tissue disorders		
	Rare:	Lupus-like syndrome
Renal and urinary disorders		
	Rare:	Bladder disorders, renal disorders
Reproductive system and breast disorders		
	Uncommon:	Breast disorders, menstrual disorders
General disorders and administration site conditions		
	Common:	Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia), chest discomfort

	Rare: Impaired healing
Injury, poisoning and procedural complications	
	Common: Bone fractures

* Observed with other TNF-blocking agents.

Throughout this section, median duration of follow-up (approximately 4 years) is generally presented for all golimumab use. Where golimumab use is described by dose, the median duration of follow-up varies (approximately 2 years for 50 mg dose, approximately 3 years for 100 mg dose) as patients may have switched between doses.

Description of selected adverse reactions

Infections
In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of golimumab-treated patients (incidence per 100 subject-years: 60.8; 95% CI: 55.0, 67.1) compared with 11.0% of control patients (incidence per 100 subject-years: 54.5; 95% CI: 46.1, 64.0). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 4 years, the incidence per 100 subject-years of upper respiratory tract infections was 34.9 events; 95% CI: 33.8, 36.0 for golimumab treated patients.

In the controlled period of pivotal trials, infections were observed in 23.0% of golimumab-treated patients (incidence per 100 subject-years: 132.0; 95% CI: 123.3, 141.1) compared with 20.2% of control patients (incidence per 100 subject-years: 122.3; 95% CI: 109.5, 136.2). In controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per 100 subject-years of infections was 81.1 events; 95% CI: 79.5, 82.8 for golimumab treated patients.

In the controlled period of RA, PsA, AS, and nr-Axial SpA trials, serious infections were observed in 1.2% of golimumab-treated patients and 1.2% of control-treated patients. The incidence of serious infections per 100 subject-years of follow-up in the controlled period of RA, PsA, AS, and nr-Axial SpA trials was 7.3; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 2.9; 95% CI: 1.2, 6.0 for the golimumab 50 mg group and 3.6; 95% CI: 1.5, 7.0 for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of golimumab-treated patients compared with 1.5% of control-treated patients. Serious infections observed in golimumab-treated patients included tuberculosis, bacterial infections including sepsis and pneumonia, invasive fungal infections and other opportunistic infections. Some of these infections have been fatal. In the controlled and uncontrolled portions of the pivotal trials with a median follow-up of up to 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 4.1; 95% CI: 3.6, 4.5, in patients receiving golimumab 100 mg and 2.5; 95% CI: 2.0, 3.1, in patients receiving golimumab 50 mg.

Malignancies
Lymphoma
The incidence of lymphoma in golimumab-treated patients during the pivotal trials was higher than expected in the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Lymphoma was diagnosed in 11 subjects (1 in the golimumab 50 mg treatment groups and 10 in the golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.03 (0.00, 0.15) and 0.13 (0.06, 0.24) events for golimumab 50 mg and 100 mg respectively and 0.00 (0.00, 0.57) events for the placebo. The majority of lymphomas occurred in study GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease (see section 4.4).

Malignancies other than lymphoma
In the controlled periods of pivotal trials and through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar to the general population.

In the controlled and uncontrolled periods of pivotal trials with a median follow-up of up to 3 years, non-melanoma skin cancer was diagnosed in 5 placebo-treated, 10 golimumab 50 mg-treated and 31 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.36 (0.26, 0.49) for combined golimumab and 0.87 (0.28, 2.04) for placebo.

In the controlled and uncontrolled period of pivotal trials with a median follow-up of up to 3 years, malignancies besides melanoma, non-melanoma skin cancer and lymphoma were diagnosed in 5 placebo-treated, 21 golimumab 50 mg-treated and 34 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.48 (0.36, 0.62) for combined golimumab and 0.87 (0.28, 2.04) for placebo (see section 4.4).

Cases reported in clinical studies in asthma
In an exploratory clinical study, patients with severe persistent asthma received a golimumab loading dose (150% of the assigned treatment dose) subcutaneously at week 0 followed by golimumab 200 mg, golimumab 100 mg or golimumab 50 mg every 4 weeks subcutaneously through week 52. Eight malignancies in the combined golimumab treatment group (n = 230) and none in the placebo treatment group (n = 79) were reported. Lymphoma was reported in 1 patient, non-melanoma skin cancer in 2 patients, and other malignancies in 5 patients. There was no specific clustering of any type of malignancy.

During the placebo-controlled portion of the study, the incidence (95% CI) of all malignancies per 100 subject-years of follow-up was 3.19 (1.38, 6.28) in the golimumab group. In this study, the incidence (95% CI) per 100 subject-years of follow-up in golimumab-treated subjects was 0.40 (0.01, 2.20) for lymphoma, 0.79 (0.10, 2.86) for non-melanoma skin cancers, and 1.99 (0.64, 4.63) for other malignancies. For placebo subjects, the incidence (95% CI) per 100 subject-years of follow-up of these malignancies was 0.00 (0.00, 2.94). The significance of this finding is unknown.

Neurological events
In the controlled and uncontrolled periods of the pivotal trials with a median follow-up of up to 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg (see section 4.4).

Liver enzyme elevations
In the controlled period of RA and PsA pivotal trials, mild ALT elevations (> 1 and < 3 x upper limit of normal (ULN)) occurred in similar proportions of golimumab and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS and nr-Axial SpA studies, more golimumab-treated patients (26.9%) than control patients (10.6%) had mild ALT elevations. In the controlled and uncontrolled periods of the RA and PsA pivotal trials, with a median follow-up of approximately 5 years, the incidence of mild ALT elevations was similar in golimumab-treated and control patients in RA and PsA studies. In the controlled period of the UC pivotal trials of golimumab induction, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of golimumab-treated and control patients (8.0% to 6.9%, respectively). In controlled and uncontrolled periods of the UC pivotal trials with a median follow-up of approximately 2 years, the proportion of patients with mild ALT elevations was 24.7% in patients receiving golimumab during the maintenance portion of the UC study.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5 x ULN were uncommon and seen in more golimumab-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. In the controlled and uncontrolled periods of RA, PsA and AS pivotal trials, with a median follow-up of 5 years, the incidence of ALT elevations ≥ 5 x ULN was

similar in both golimumab-treated and control patients. In general these elevations were asymptomatic and the abnormalities decreased or resolved with either continuation or discontinuation of golimumab or modification of concomitant medicinal products. No cases were reported in the controlled and uncontrolled periods of the nr-Axial SpA study (up to 1 year). In the controlled periods of the pivotal UC trials, of golimumab induction, ALT elevations ≥ 5 x ULN occurred in similar proportions of golimumab-treated patients compared to placebo-treated patients (0.3% to 1.0%, respectively). In the controlled and uncontrolled periods of the pivotal UC trials with a median follow-up of approximately 2 years, the proportion of patients with ALT elevations ≥ 5 x ULN was 0.8% in patients receiving golimumab during the maintenance portion of the UC study.

Within the RA, PsA, AS, and nr-Axial SpA pivotal trials, one patient in an RA trial with pre-existing liver abnormalities and confounding medicinal products treated with golimumab developed non-infectious fatal hepatitis with jaundice. The role of golimumab as a contributing or aggravation factor cannot be excluded.

Injection site reactions
In the controlled periods of pivotal trials, 5.4% of golimumab-treated patients had injection site reactions compared with 2.0% in control patients. The presence of antibodies to golimumab may increase the risk of injection site reactions. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

In controlled Phase IIb and/or III trials in RA, PsA, AS, nr-Axial SpA, severe persistent asthma, and Phase II/III trials in UC, no patients treated with golimumab developed anaphylactic reactions.

Autoimmune antibodies
In the controlled and uncontrolled periods of pivotal trials through 1 year of follow-up, 3.5% of golimumab-treated patients and 2.3% of control patients were newly ANA-positive (at titres of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients anti-dsDNA negative at baseline was 1.1%.

Paediatric population
Polyarticular juvenile idiopathic arthritis
The safety of golimumab has been studied in a Phase III study of 173 pJIA patients from 2 to 17 years of age. The average follow-up was approximately two years. In this study, the type and frequency of adverse events reported were generally similar to those seen in adult RA studies.

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

Single doses up to 10 mg/kg intravenously have been administered in a clinical study without dose-limiting toxicity. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors, ATC code: L04AB06

Mechanism of action
Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors.

Pharmacodynamic effects
The binding of human TNF by golimumab was shown to neutralise TNF-α-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. *In vitro*, TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab.

Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with Simponi resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix-metalloproteinase (MMP)-3 and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNF-α were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients. These changes were observed at the first assessment (week 4) after the initial Simponi administration and were generally maintained through week 24.

Clinical efficacy

Adult rheumatoid arthritis
The efficacy of Simponi was demonstrated in three multi-centre, randomised, double-blind, placebo-controlled studies in over 1500 patients ≥ 18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening. Patients had at least 4 swollen and 4 tender joints. Simponi or placebo were subcutaneously administered every 4 weeks.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. Patients receiving placebo + MTX were switched to Simponi 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

GO-AFTER evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomised to receive placebo, Simponi 50 mg, or Simponi 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Simponi 50 mg + MTX.

In GO-FORWARD, the (co-) primary endpoints were the percentage of patients achieving an ACR 20 response at week 14 and the improvement from baseline in Health Assessment Questionnaire (HAQ) at week 24. In GO-AFTER, the primary endpoint was the percentage of patients achieving an ACR 20 response at week 14. In GO-BEFORE, the co-primary endpoints were the percentage of patients achieving ACR 50 response at week 24 and the change from baseline in the van der Heijde-modified Sharp (vdH-S) score at week 52. In addition to the primary endpoint(s), additional assessments of the impact of Simponi treatment on the signs and symptoms of arthritis, radiographic response, physical function and health-related quality of life were performed.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens with concomitant MTX, through week 104 in GO-FORWARD and GO-BEFORE and through week 24 in GO-AFTER. In each of the RA studies by study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms

Key ACR results for the Simponi 50 mg dose at weeks 14, 24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 2 and are described below. Responses were observed at the first assessment (week 4) after the initial Simponi administration.

In GO-FORWARD, among 89 subjects randomised to Simponi 50 mg + MTX, 48 were still on this treatment at week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving Simponi than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 2
Key efficacy outcomes from the controlled portions of GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	Simponi 50 mg + MTX	Placebo	Simponi 50 mg	Placebo + MTX	Simponi 50 mg + MTX
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA
Week 24	28%	60%*	16%	31% p = 0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p = 0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p = 0.008	2%	10% p = 0.005	NA	NA
Week 24	5%	20%*	2%	9% p = 0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.
* $p \leq 0.001$
NA: Not Applicable

In GO-BEFORE the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Simponi 50 and 100 mg + MTX groups vs MTX alone for ACR50) was not statistically significant at week 24 (p = 0.053). At week 52 in the overall population, the percentage of patients in the Simponi 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 2). Additional analyses were performed in subsets representative of the indicated population of patients with severe, active and

progressive RA. A generally greater effect of Simponi 50 mg + MTX versus MTX alone was demonstrated in the indicated population compared with the overall population.

In GO-FORWARD and GO-AFTER, clinically meaningful and statistically significant responses in Disease Activity Scale (DAS)28 were observed at each prespecified time point, at week 14 and at week 24 ($p \leq 0.001$). Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 responses were similar from week 104 through week 256.

In GO-BEFORE, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At week 52, 15% of patients in the Simponi 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group ($p = 0.018$). Among 159 subjects randomised to Simponi 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response were observed from week 104 through week 256.

Radiographic response

In GO-BEFORE the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Simponi 50 mg dose at week 52 are presented in Table 3.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the Simponi treatment group than in the control group ($p = 0.003$). The radiographic effects observed at week 52 were maintained through week 104. Among patients remaining in the study and treated with Simponi, radiographic effects were similar from week 104 through week 256.

Table 3
Radiographic mean (SD) changes from baseline in total vdH-S score at week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Simponi 50 mg + MTX**
n[a]	**160**	**159**
Total Score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion Score		
Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.7 (2.8)	0.5 (2.1)
JSN Score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)**

[a] n reflects randomised patients

* $p = 0.015$

** $p = 0.044$

Physical function and health-related quality of life

Physical function and disability were assessed as a separate endpoint in GO-FORWARD and GO-AFTER using the disability index of the HAQ DI. In these studies, Simponi demonstrated clinically meaningful and statistically significant improvement in HAQ DI from baseline versus control at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement in HAQ DI was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement in HAQ DI was similar from week 104 through week 256.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with Simponi versus placebo at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement of the SF-36 physical component was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement of the SF-36 physical component was similar from week 104 through week 256. In GO-FORWARD and GO-AFTER, statistically significant improvements were observed in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F).

Adult psoriatic arthritis
The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months and had at least mild psoriatic disease. Patients with each sub-type of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). Previous treatment with an anti-TNF agent was not allowed. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg, or Simponi 100 mg. Patients receiving placebo were switched to Simponi 50 mg after week 24. Patients entered an open label long-term extension at week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at week 14 and change from baseline in total PsA modified vdH-S score at week 24.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 104. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms
Key results for the 50 mg dose at weeks 14 and 24 are shown in Table 4 and described below.

Table 4
Key efficacy outcomes from GO-REVEAL

	Placebo	Simponi 50 mg*
n[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	**9%**	**51%**
Week 24	12%	52%
ACR 50		
Week 14	2%	30%
Week 24	4%	32%
ACR 70		
Week 14	1%	12%
Week 24	1%	19%
PASI[b] 75[c]		
Week 14	3%	40%
Week 24	1%	56%

* $p < 0.05$ for all comparisons;

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

[b] *Psoriasis Area and Severity Index*

[c] Based on the subset of patients with ≥ 3% BSA involvement at baseline, 79 patients (69.9%) in the placebo group and 109 (74.3%) in the Simponi 50 mg group.

Responses were observed at the first assessment (week 4) after the initial Simponi administration. Similar ACR 20 responses at week 14 were observed in patients with polyarticular arthritis with no rheumatoid nodules and asymmetric peripheral arthritis PsA subtypes. The number of patients with other PsA subtypes was too small to allow meaningful assessment. Responses observed in the Simponi treated groups were similar in patients receiving and not receiving concomitant MTX. Among 146 patients randomised to Simponi 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 ($p < 0.05$).

At week 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Simponi-treated patients. Simponi treatment resulted in significant improvement in physical function as assessed by HAQ DI, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36. Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 and HAQ DI responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 and HAQ DI responses were similar from week 104 through week 256.

Radiographic response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the vdH-S score, modified for PsA by addition of hand distal interphalangeal (DIP) joints.

Simponi 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean ± SD score was 0.27 ± 1.3 in the placebo group compared with -0.16 ± 1.3 in the Simponi group; $p = 0.011$). Out of 146 patients who were randomised to Simponi 50 mg, 52 week X-ray data were available for 126 patients, of whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline. Among patients remaining in the study and treated with Simponi, similar rates of patients showed no progression from baseline from week 104 through week 256.

Adult axial spondyloarthritis

Adult ankylosing spondylitis

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and a VAS for total back pain of ≥ 4, on a scale of 0 to 10 cm). Patients enrolled in this study had active disease despite current or previous NSAID or DMARD therapy and had not previously been treated with anti-TNF therapy. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg and Simponi 100 mg and were allowed to continue concomitant DMARD therapy (MTX, SSZ and/or HCQ). The primary endpoint was the percentage of patients achieving Ankylosing Spondylitis Assessment Study Group (ASAS) 20 response at week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

Key results for the 50 mg dose are shown in Table 5 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 24. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Table 5
Key efficacy outcomes from GO-RAISE

	Placebo	Simponi 50 mg*
n[a]	78	138
Responders, % of patients		
ASAS 20		
Week 14	**22%**	**59%**
Week 24	23%	56%
ASAS 40		
Week 14	15%	45%
Week 24	15%	44%
ASAS 5/6		
Week 14	8%	50%
Week 24	13%	49%

* $p \leq 0.001$ for all comparisons

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

Among patients remaining in the study and treated with Simponi, the proportion of patients with an ASAS 20 and ASAS 40 response were similar from week 24 through week 256.

Statistically significant responses in BASDAI 50, 70 and 90 ($p \leq 0.017$) were also seen at weeks 14 and 24. Improvements in key measures of disease activity were observed at the first assessment (week 4) after the initial Simponi administration and were maintained through week 24. Among patients remaining in the study and treated with Simponi, similar rates of change from baseline in BASDAI were observed from week 24 through week 256. Consistent efficacy was seen in patients regardless of use of DMARDs (MTX, sulfasalazine and/or hydroxychloroquine), HLA-B27 antigen status or baseline CRP levels as assessed by ASAS 20 responses at week 14.

Simponi treatment resulted in significant improvements in physical function as assessed by changes from baseline in BASFI at weeks 14 and 24. Health-related quality of life as measured by the physical component score of the SF-36 was also improved significantly at weeks 14 and 24. Among patients remaining in the study and treated with Simponi, improvements in physical function and health-related quality of life were similar from week 24 through week 256.

Adult non-radiographic axial spondyloarthritis

GO-AHEAD

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-AHEAD) in 197 adult patients with severe active nr-Axial SpA (defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS). Patients enrolled in this study had active disease (defined as a BASDAI ≥ 4 and a Visual Analogue Scale (VAS) for total back pain of ≥ 4, each on a scale of 0-10 cm) despite current or previous NSAID therapy and had not previously been treated with any biological agents including anti-TNF therapy. Patients were randomly assigned to placebo or Simponi 50 mg administered subcutaneously every 4 weeks. At week 16, patients entered an open label period in which all patients received Simponi 50 mg administered subcutaneously every 4 weeks through week 48 with efficacy assessments performed through week 52 and safety follow-up through week 60. Approximately 93% of patients who were receiving Simponi at the beginning of the open-label extension (week 16) remained on treatment through the end of the study (week 52). Analyses were performed on both the All Treated (AT, N = 197) and Objective Signs of Inflammation (OSI, N = 158, defined by elevated CRP and/or evidence of sacroiliitis on MRI at baseline) populations. Placebo-controlled efficacy data were collected and analysed through week 16. The primary endpoint was the proportion of patients achieving ASAS 20 response at week 16. Key results are shown in Table 6 and described below.

Table 6
Key efficacy outcomes from GO-AHEAD at week 16

Improvements in signs and symptoms				
	All treated population (AT)		Objective signs of inflammation population (OSI)	
	Placebo	Simponi 50 mg	Placebo	Simponi 50 mg
n[a]	100	97	80	78
Responders, % of patients				
ASAS 20	40%	71%**	38%	77%**
ASAS 40	23%	57%**	23%	60%**
ASAS 5/6	23%	54%**	23%	63%**
ASAS Partial Remission	18%	33%*	19%	35%*
ASDAS-C[b] < 1.3	13%	33%*	16%	35%*
BASDAI 50	30%	58%**	29%	59%**
Inhibition of inflammation in sacroiliac (SI) joints as measured by MRI				
	Placebo	Simponi 50 mg	Placebo	Simponi 50 mg
n[c]	87	74	69	61
Mean change in SPARCC[d] MRI sacroiliac joint score	-0.9	-5.3**	-1.2	-6.4**

[a] n reflects randomised and treated patients

[b] Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (AT-Placebo, N = 90; AT-Simponi 50 mg, N = 88; OSI-Placebo, N = 71; OSI-Simponi 50 mg, N = 71)

[c] n reflects number of patients with baseline and week 16 MRI data

[d] SPARCC (Spondyloarthritis Research Consortium of Canada)

** $p < 0.0001$ for Simponi *vs* placebo comparisons

* $p < 0.05$ for Simponi *vs* placebo comparisons

Statistically significant improvements in signs and symptoms of severe active nr-Axial SpA were demonstrated in patients treated with Simponi 50 mg compared to placebo at week 16 (Table 6). Improvements were observed at the first assessment (week 4) after the initial Simponi administration. SPARCC score as measured by MRI showed statistically significant reductions in SI joint inflammation at week 16 in patients treated with Simponi 50 mg compared to placebo (Table 6). Pain as assessed by the Total Back Pain and Nocturnal Back Pain VAS, and disease activity as measured by ASDAS-C also showed statistically significant improvement from baseline to week 16 in patients treated with Simponi 50 mg compared to placebo ($p < 0.0001$).

Statistically significant improvements in spinal mobility as assessed by BASMI (Bath Ankylosing Spondylitis Metrology Index) and in physical function as assessed by the BASFI were demonstrated in Simponi 50 mg-treated patients as compared to placebo-treated patients ($p < 0.0001$). Patients treated with Simponi experienced significantly more improvements in health-related quality of life as assessed by ASQoL, EQ-5D, and physical and mental components of SF-36, and experienced significantly more improvements in productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI questionnaire than patients receiving placebo.

For all of the endpoints described above, statistically significant results were also demonstrated in the OSI population at week 16.

In both the AT and OSI populations, the improvements in signs and symptoms, spinal mobility, physical function, quality of life, and productivity observed at week 16 among patients treated with Simponi 50 mg continued in those remaining in the study at week 52.

GO-BACK

The efficacy and safety of continued golimumab treatment (full or reduced dosing frequency) compared with treatment withdrawal was assessed in adult patients (18-45 years of age) with active

nr-axSpA who demonstrated sustained remission during 10 months of monthly treatment with open-label Simponi (GO-BACK). Eligible patients (who achieved a clinical response by Month 4 and an inactive disease status (ASDAS < 1.3) at both Months 7 and 10) entering the double-blind withdrawal phase were randomised to continued monthly treatment with Simponi (full-treatment regimen, N = 63), every 2-month treatment with Simponi (reduced treatment regimen, N = 63) or monthly placebo treatment (treatment withdrawal, N = 62) for up to approximately 12 months.

The primary efficacy endpoint was the proportion of patients without a flare of disease activity. Patients who experienced a flare, i.e., had an ASDAS collected at 2 consecutive assessments that both showed either an absolute score of ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (end of open-label period), reinitiated monthly Simponi in an open-label retreatment phase to characterise clinical response.

Clinical response after double-blind treatment withdrawal
Among the 188 patients with inactive disease who received at least one dose of double-blind treatment, a significantly ($p < 0.001$) greater proportion of patients did not experience a disease flare when continuing Simponi with either the full-treatment (84.1%), or reduced treatment (68.3%) regimens compared with treatment withdrawal (33.9%) (Table 7).

Table 7
Analysis of the proportion of participants without a flare[a]
Full analysis set population (Period 2 – Double-blind)

			Difference in % vs Placebo	
Treatment	**n/N**	**%**	**Estimate (95% CI)[b]**	**p-Value[b]**
GLM SC QMT	53/63	84.1	50.2 (34.1, 63.6)	< 0.001
GLM SC Q2MT	43/63	68.3	34.4 (17.0, 49.7)	< 0.001
Placebo	21/62	33.9		

Full Analysis Set includes all randomised participants who attained inactive disease in period 1 and received at least one dose of blinded study treatment.

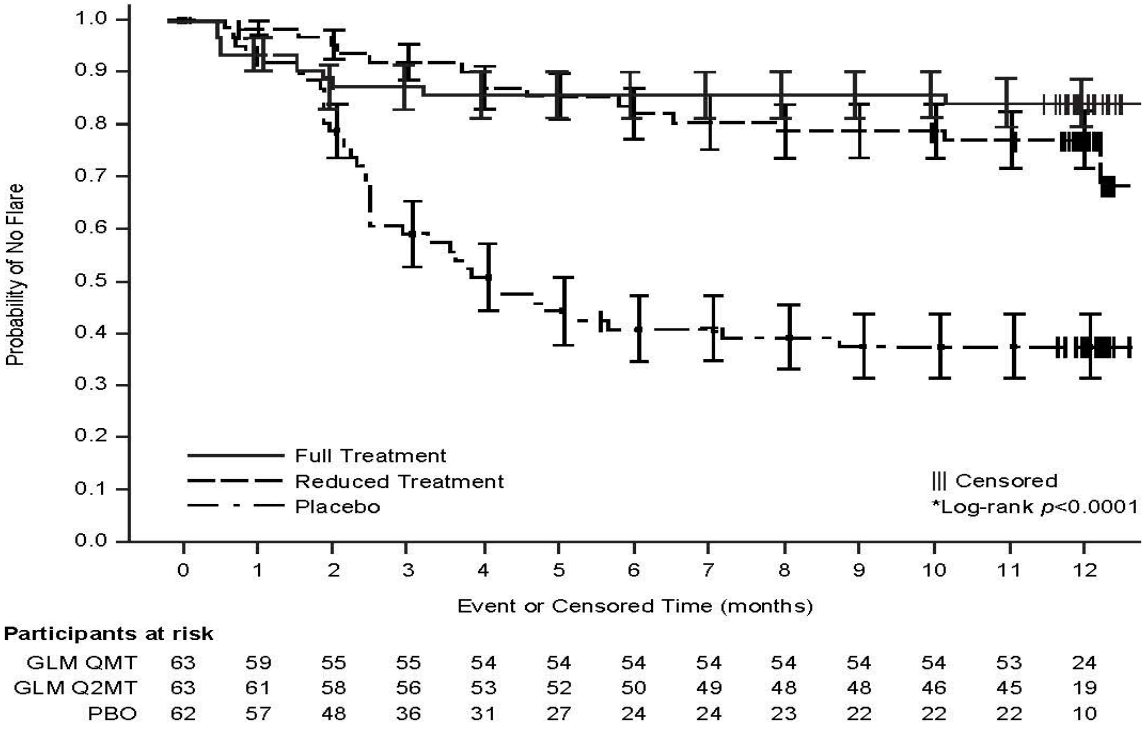
[a] Defined as ASDAS at 2 consecutive visits that both show either absolute score ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23).

[b] Type I error rate over the multiple treatment comparisons (GLM SC QMT vs Placebo and GLM SC Q2MT vs Placebo) was controlled using a sequential (step-down) testing procedure. Derived based on the stratified Miettinen and Nurminen method with CRP level (> 6 mg/L or ≤ 6 mg/L) as stratification factor.

Participants who discontinued period 2 prematurely and prior to a 'flare' will be counted as having a 'flare'.
N = Total number of participants; n = number of participants without a flare; GLM = golimumab; SC = subcutaneous, QMT = monthly dosing; Q2MT = every other month dosing.

The difference in time-to-first flare between the treatment withdrawal group and either of the Simponi Treatment groups is shown in Figure 1 (log-rank $p < 0.0001$ for each comparison). In the placebo group, flares started approximately 2 months after Simponi was withdrawn, with the majority of flares occurring within 4 months of treatment withdrawal (Figure 1).

Figure 1: Kaplan-Meier Analysis of Time-to-First Flare



Participants at risk

GLM QMT	63	59	55	55	54	54	54	54	54	54	54	53	24
GLM Q2MT	63	61	58	56	53	52	50	49	48	48	46	45	19
PBO	62	57	48	36	31	27	24	24	23	22	22	22	10

*Endpoint not adjusted for multiplicity. Stratified by CRP level (> 6 mg/L or ≤ 6 mg/L). Flare was defined as an ASDAS at 2 consecutive visits that both showed either an absolute score of ≥ 2.1 or a post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23). Participants who did not flare were censored at the time of discontinuation or Month 13 of Period 2 double-blind treatment. Start of Period 2 represents Day 1 of the Kaplan-Meier analysis for the full analysis set.

Clinical response to retreatment for a disease flare
Clinical response was defined as a BASDAI improvement of ≥ 2 or ≥ 50% relative to the mean of the 2 consecutive BASDAI scores ascribed to the disease flare. Of the 53 participants in the reduced dosing or treatment withdrawal regimens who had a confirmed disease flare, 51 (96.2%) attained a clinical response to Simponi within the first 3 months of retreatment, although fewer patients (71.7%) were able to sustain it for all 3 months.

Adult ulcerative colitis
The efficacy of Simponi was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients.

The induction study (PURSUIT-Induction) evaluated patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) who had an inadequate response to or failed to tolerate conventional therapies, or were corticosteroid dependent. In the dose confirming portion of the study, 761 patients were randomised to receive either 400 mg Simponi SC at week 0 and 200 mg at week 2, 200 mg Simponi SC at week 0 and 100 mg at week 2, or placebo SC at weeks 0 and 2. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. The efficacy of Simponi through week 6 was assessed in this study.

The results of the maintenance study (PURSUIT-Maintenance) were based on evaluation of 456 patients who achieved clinical response from previous induction with Simponi. Patients were randomised to receive Simponi 50 mg, Simponi 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, and/or immunomodulatory agents were permitted. Corticosteroids were to be tapered at the start of the maintenance study. The efficacy of Simponi through week 54 was assessed in this study. Patients who completed the maintenance study through week 54 continued treatment in a study extension, with efficacy evaluated through week 216. Efficacy evaluation in the study extension was based on changes in corticosteroid use, Physician's

Global Assessment (PGA) of disease activity, and improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire (IBDQ).

Table 8
Key efficacy outcomes from PURSUIT - Induction and PURSUIT - Maintenance

PURSUIT-Induction			
	Placebo N = 251	**Simponi 200/100 mg** N = 253	
Percentage of patients			
Patients in clinical response at week 6[a]	30%	51%**	
Patients in clinical remission at week 6[b]	6%	18%**	
Patients with mucosal healing at week 6[c]	29%	42%*	
PURSUIT-Maintenance			
	Placebo[d] N = 154	**Simponi 50 mg** N = 151	**Simponi 100 mg** N = 151
Percentage of patients			
Maintenance of response (Patients in clinical response through week 54)[e]	31%	47%*	50%**
Sustained remission (Patients in clinical remission at both week 30 and week 54)[f]	16%	23%[g]	28%*

N = number of patients
** $p \leq 0.001$
* $p \leq 0.01$
[a] defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.
[b] Defined as a Mayo score ≤ 2 points, with no individual subscore > 1
[c] Defined as 0 or 1 on the endoscopy subscore of the Mayo score.
[d] Simponi induction only.
[e] Patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). Therefore, a patient who maintained response was in a state of continuous clinical response at each evaluation through week 54.
[f] A patient had to be in remission at both weeks 30 and 54 (without demonstrating a loss of response at any time point through week 54) to achieve durable remission.
[g] In patients weighing less than 80 kg, a greater proportion of patients who received 50 mg maintenance therapy showed sustained clinical remission compared with those who received placebo.

More Simponi-treated patients demonstrated sustained mucosal healing (patients with mucosal healing at both week 30 and week 54) in the 50 mg group (42%, nominal $p < 0.05$) and 100 mg group (42%, $p < 0.005$) compared with patients in the placebo group (27%).

Among the 54% of patients (247/456) who were receiving concomitant corticosteroids at the start of PURSUIT-Maintenance, the proportion of patients who maintained clinical response through week 54 and were not receiving concomitant corticosteroids at week 54 was greater in the 50 mg group (38%, 30/78) and 100 mg group (30%, 25/82) compared with the placebo group (21%, 18/87). The proportion of patients who eliminated corticosteroids by week 54 was greater in the 50 mg group (41%, 32/78) and 100 mg group (33%, 27/82) compared with the placebo group (22%, 19/87). Among patients who entered the study extension, the proportion of subjects who remained corticosteroid free was generally maintained through week 216.

Patients who did not achieve clinical response at week 6 in the PURSUIT-Induction studies were dosed Simponi 100 mg every 4 weeks in the PURSUIT-Maintenance study. At week 14, 28% of these patients achieved response defined by partial Mayo score (decreased by ≥ 3 points compared with start of induction). At week 54, the clinical outcomes observed in these patients were similar to the clinical outcomes reported for the patients achieving clinical response at week 6.

At week 6, Simponi significantly improved quality of life as measured by change from baseline in a disease specific measure, IBDQ (inflammatory bowel disease questionnaire). Among patients who received Simponi maintenance treatment, the improvement in quality of life as measured by IBDQ was maintained through week 54.

Approximately 63% of patients who were receiving Simponi at the beginning of the study extension (week 56), remained on treatment through the end of the study (last golimumab administration at week 212).

Immunogenicity

Across the Phase III RA, PsA and AS studies through week 52, antibodies to golimumab were detected by the enzyme immunoassay (EIA) method in 5% (105/2062) of golimumab treated patients and, where tested, nearly all antibodies were neutralising *in vitro*. Similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without MTX (approximately 3% [41/1235] versus 8% [64/827], respectively).

In nr-Axial SpA, antibodies to golimumab were detected in 7% (14/193) of golimumab treated patients through week 52 by the EIA method.

In the Phase II and III UC studies through week 54, antibodies to golimumab were detected by the EIA method in 3% (26/946) of golimumab treated patients. Sixty-eight percent (21/31) of antibody-positive patients had neutralising antibodies *in vitro*. Treatment with concomitant immunomodulators (azathioprine, 6-mercaptopurine and MTX) resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without immunomodulators (1% (4/308) versus 3% (22/638), respectively). Of patients that continued in the study extension and had evaluable samples through week 228, antibodies to golimumab were detected in 4% (23/604) of golimumab treated patients. Eighty-two percent (18/22) of antibody-positive patients had neutralising antibodies *in vitro*.

A drug-tolerant EIA method was used in the pJIA study for the detection of antibodies to golimumab. Due to the higher sensitivity and the improved drug tolerance, a higher incidence of antibodies to golimumab was expected to be detected with the drug-tolerant EIA method compared to the EIA method. In the Phase III pJIA study through week 48, antibodies to golimumab were detected by the drug-tolerant EIA method in 40% (69/172) of golimumab treated children of which a majority had a titre lower than 1:1000. An effect on serum golimumab concentrations was seen at titres of > 1:100 while an effect on efficacy was not seen until titres of > 1:1000, though the numbers of children with titres of > 1:1000 were low (N = 8). Among the children who tested positive for antibodies to golimumab, 39% (25/65) had neutralising antibodies. The higher incidence of antibodies with the drug-tolerant EIA method, because they were mainly low titre antibodies, did not have an apparent impact on drug levels, efficacy and safety and therefore does not represent any new safety signal.

The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.8). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

Because immunogenicity analyses are product- and assay-specific, comparison of antibody rates with those from other products is not appropriate.

Paediatric population

Paediatric polyarticular juvenile idiopathic arthritis

The safety and efficacy of Simponi was evaluated in a randomised, double-blind, placebo-controlled, withdrawal study (GO-KIDS) in 173 children (2 to 17 years of age) with active pJIA with at least 5 active joints and an inadequate response to MTX. Children with polyarticular course JIA

(rheumatoid factor positive or negative polyarthritis, extended oligoarthritis, juvenile psoriatic arthritis or systemic JIA with no current systemic symptoms) were included in the study. The baseline median number of active joints was 12, and median CRP was 0.17 mg/dL.

Part 1 of the study consisted of a 16-week open-label phase in which 173 enrolled children received Simponi 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks and MTX. The 154 children who achieved an ACR Ped 30 response at week 16 entered Part 2 of the study, the randomised withdrawal phase, and received Simponi 30 mg/m^2 (maximum 50 mg) + MTX or placebo + MTX every 4 weeks. After disease flare, children received Simponi 30 mg/m^2 (maximum 50 mg) + MTX. At week 48, children entered a long-term extension.

Children in this study demonstrated ACR Ped 30, 50, 70, and 90 responses from week 4.

At week 16, 87% of children were ACR Ped 30 responders, and 79%, 66%, and 36% of children were ACR Ped 50, ACR Ped 70, and ACR Ped 90 responders, respectively. At week 16, 34% of children had inactive disease defined as having the presence of all of the following: no joints with active arthritis; no fever, rash, serositis, splenomegaly, hepatomegaly, or generalised lymphadenopathy attributable to JIA; no active uveitis; normal ESR (< 20 mm/hour) or CRP (< 1.0 mg/dL); physician global assessment of disease activity (≤ 5 mm on the VAS); duration of morning stiffness < 15 minutes.

At week 16, all ACR Ped components demonstrated clinically relevant improvement from baseline (see Table 9).

Table 9
Improvements from baseline in ACR Ped components at week 16[a]

	Median percent improvement
	Simponi 30 mg/m^2 n[b] = 173
Physicians global assessment of disease (VAS[c] 0-10 cm)	88%
Subject/parent global assessment of overall well-being (VAS 0-10 cm)	67%
Number of active joints	92%
Number of joints with limited range of motion	80%
Physical function by CHAQ[d]	50%
ESR (mm/h)[e]	33%

[a] baseline = week 0
[b] "n" reflects enrolled patients
[c] VAS: Visual Analogue Scale
[d] CHAQ: Child Health Assessment Questionnaire
[e] ESR (mm/h): erythrocyte sedimentation rate (millimetres per hour)

The primary endpoint, the proportion of children who were ACR Ped 30 responders at week 16 and who did not experience a flare between week 16 and week 48, was not achieved. The majority of children did not experience a flare between week 16 and week 48 (59% in the Simponi + MTX and 53% in the placebo + MTX groups, respectively; p = 0.41).

Pre-specified subgroup analyses of the primary endpoint by baseline CRP (≥ 1 mg/dL vs < 1 mg/dL) demonstrated higher flare rates in placebo + MTX vs Simponi + MTX treated subjects among subjects with baseline CRP ≥ 1 mg/dL (87% vs 40% p = 0.0068).

At week 48, 53% and 55% of children in the Simponi + MTX group and placebo + MTX group, respectively, were ACR Ped 30 responders, and 40% and 28% of children in the Simponi + MTX group and placebo + MTX group, respectively, achieved inactive disease.

5.2 Pharmacokinetic properties

Absorption
Following a single subcutaneous administration of golimumab to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A subcutaneous injection of 50 mg golimumab to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/mL.

Following a single subcutaneous injection of 100 mg, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since golimumab exhibited approximately dose proportional PK following a subcutaneous administration, the absolute bioavailability of a golimumab 50 mg or 200 mg dose is expected to be similar.

Distribution
Following a single IV administration, the mean volume of distribution was 115 ± 19 mL/kg.

Elimination
The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg. Terminal half-life value was estimated to be approximately 12 ± 3 days in healthy subjects and similar values were observed in patients with RA, PsA, AS, or UC.

When 50 mg golimumab was administered subcutaneously to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by week 12. With concomitant use of MTX, treatment with 50 mg golimumab subcutaneously every 4 weeks resulted in a mean (± standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 μg/mL in patients with active PsA and approximately 0.8 ± 0.4 μg/mL in patients with AS. Steady-state trough mean serum golimumab concentrations in patients with nr-Axial SpA were similar to those observed in patients with AS following subcutaneous administration of 50 mg golimumab every 4 weeks.

Patients with RA, PsA or AS who did not receive concomitant MTX had approximately 30% lower steady-state trough concentrations of golimumab than those who received golimumab with MTX. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. However, population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

Following induction doses of 200 mg and 100 mg golimumab at week 0 and 2, respectively, and maintenance doses of 50 mg or 100 mg golimumab subcutaneously every 4 weeks thereafter to patients with UC, serum golimumab concentrations reached steady state approximately 14 weeks after the start of therapy. Treatment with 50 mg or 100 mg golimumab subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 0.9 ± 0.5 μg/mL and 1.8 ± 1.1 μg/mL, respectively.

In UC patients treated with 50 mg or 100 mg golimumab subcutaneously every 4 weeks, concomitant use of immunomodulators did not have a substantial effect on steady-state trough levels of golimumab.

Patients who developed antibodies to golimumab generally had low trough steady-state serum concentrations of golimumab (see section 5.1).

Linearity
Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose. Following a single SC dose in healthy subjects, approximately dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg.

Effect of weight on pharmacokinetics
There was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

Paediatric population
Polyarticular juvenile idiopathic arthritis
The pharmacokinetics of golimumab were determined in 173 children with pJIA with an age range from 2 to 17 years of age. In the pJIA study, children who received golimumab 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks, had median steady-state trough golimumab concentrations which were similar across different age groups, and which were also similar to or slightly higher than those seen in adult RA patients who received 50 mg golimumab every 4 weeks.

Population pharmacokinetic/pharmacodynamic modelling and simulation in children with pJIA confirmed the relationship between golimumab serum exposures and clinical efficacy and supports that the dosing regimen of golimumab 50 mg every 4 weeks in children with pJIA of at least 40 kg achieves similar exposures to those shown to be efficacious in adults.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

No mutagenicity studies, animal fertility studies nor long-term carcinogenic studies have been conducted with golimumab.

In a fertility and general reproductive function study in mouse, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, the number of pregnant mice was reduced. It is not known whether this finding was due to effects on the males and/or the females. In a developmental toxicity study conducted in mice following administration of the same analogous antibody, and in cynomolgus monkeys using golimumab, there was no indication of maternal toxicity, embryotoxicity or teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years

6.4 Special precautions for storage

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

Keep the pre-filled pen in the outer carton in order to protect it from light.
Simponi may be stored at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 30 days from the date removed from the refrigerator).

Once Simponi has been stored at room temperature, it should not be returned to refrigerated storage. Simponi must be discarded if not used within the 30 days of room temperature storage.

6.5 Nature and contents of container

Simponi 50 mg solution for injection in pre-filled pen
0.5 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex) in a pre-filled pen. Simponi is available in packs containing 1 pre-filled pen and multipacks containing 3 (3 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Simponi is supplied in a single use pre-filled pen called SmartJect. Each pack is provided with instructions for use that fully describe the use of the pen. After removing the pre-filled pen from the refrigerator it should be allowed to reach room temperature by waiting for 30 minutes, before injecting Simponi. The pen should not be shaken.

The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for solutions containing protein. Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

Comprehensive instructions for the preparation and administration of Simponi in a pre-filled pen are given in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/001 1 pre-filled pen
EU/1/09/546/002 3 pre-filled pens

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 October 2009
Date of latest renewal: 19 June 2014

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

Simponi 100 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL pre-filled syringe contains 100 mg of golimumab*.

* Human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology.

Excipients with known effect
Each pre-filled syringe contains 41 mg sorbitol (E420) per 100 mg dose.

Each pre-filled syringe contains 0.15 mg of polysorbate 80 (E433) per 100 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)
Simponi, in combination with methotrexate (MTX), is indicated for:
- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

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

For information regarding the polyarticular juvenile idiopathic arthritis indication, please see the Simponi 50 mg SmPC.

Psoriatic arthritis (PsA)
Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Simponi has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Axial spondyloarthritis
Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)
Simponi is indicated for the treatment of adults with severe, active 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, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)
Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis (pUC)
Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients 2 years of age and older with a body weight of at least 15 kg, who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

4.2 Posology and method of administration

Treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis. Patients treated with Simponi should be given the Patient Card.

Posology

Rheumatoid arthritis
Simponi 50 mg given once a month, on the same date each month.
Simponi should be given concomitantly with MTX.

Psoriatic arthritis, ankylosing spondylitis, or non-radiographic axial spondyloarthritis
Simponi 50 mg given once a month, on the same date each month.

For all of the above indications, available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Patients with body weight greater than 100 kg
For all of the above indications, in patients with RA, PsA, AS, or nr-Axial SpA with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse reactions with the 100 mg dose compared with the 50 mg dose (see section 4.8). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

Adult ulcerative colitis
Patients with body weight less than 80 kg
Simponi given as an initial dose of 200 mg, followed by 100 mg at week 2. Patients who have an adequate response should receive 50 mg at week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter (see section 5.1).

Patients with body weight greater than or equal to 80 kg
Simponi given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter (see section 5.1).

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Paediatric ulcerative colitis (pUC)
The recommended dose of Simponi for patients from 2 to 17 years of age with ulcerative colitis is based on body weight (Table 1). Simponi is administered via subcutaneous injection.

Table 1: Simponi dose for paediatric patients with ulcerative colitis

Patient weight	Induction Dose	Maintenance Dose Starting at Week 6	Optional Maintenance Dose reduction*
≥80 kg	• 200 mg at week 0 and • 100 mg at week 2	• 100 mg every four weeks	Not applicable
≥40 kg to <80 kg	• 200 mg at week 0 and • 100 mg at week 2	• 100 mg every four weeks	• 50 mg every four weeks
≥15 kg to <40 kg	• 100 mg at week 0 and • 50 mg at week 2	• 50 mg every four weeks	• 25 mg every four weeks

* The physician may consider decreasing the maintenance dose for patients who are in remission at or after week 54.

For the posology and administration of 25 mg of golimumab, refer to section 4.2 of the 45 mg/0.45 mL solution for injection in pre-filled pen SmPC.
For the posology and administration of 50 mg of golimumab, refer to section 4.2 of the 50 mg solution for injection in pre-filled syringe SmPC.

Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in children who show no evidence of therapeutic benefit within this time period.

Missed dose
If a patient forgets to inject Simponi on the planned date, the forgotten dose should be injected as soon as the patient remembers. Patients should be instructed not to inject a double dose to make up for the forgotten dose.

The next dose should be administered based on the following guidance:
- if the dose is less than 2 weeks late, the patient should inject the forgotten dose and stay on the original schedule.
- if the dose is more than 2 weeks late, the patient should inject the forgotten dose and a new schedule should be established from the date of this injection.

Special populations
Elderly (≥ 65 years)
No dose adjustment is required in the elderly.

Renal and hepatic impairment
Simponi has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of Simponi in patients aged less than 18 for indications other than pJIA and pUC have not been established. No data are available. There is no relevant use of Simponi in children aged less than 2 years in pJIA or pUC.

Method of administration
Simponi is for subcutaneous use. After proper training in subcutaneous injection technique, patients may self-inject if their physician determines that this is appropriate, with medical follow-up as

necessary. Patients should be instructed to inject the full amount of Simponi according to the comprehensive instructions for use provided in the package leaflet. If multiple injections are required, the injections should be administered at different sites on the body. Each pre-filled syringe is for single use in a single patient, and should be discarded immediately after use.

For administration instructions, see section 6.6.

4.3 Contraindications

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

Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate or severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Patients must be monitored closely for infections including tuberculosis before, during and after treatment with golimumab. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. Further treatment with golimumab must not be given if a patient develops a serious infection or sepsis (see section 4.3).

Golimumab should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of golimumab in patients with a chronic infection or a history of recurrent infection. Patients should be advised of, and avoid exposure to, potential risk factors for infection as appropriate.

Patients taking TNF-blockers are more susceptible to serious infections.
Bacterial (including sepsis and pneumonia), mycobacterial (including TB), invasive fungal and opportunistic infections, including fatalities, have been reported in patients receiving golimumab. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with golimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of golimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of golimumab treatment should be carefully considered before initiation of golimumab therapy. In at-risk patients treated with golimumab, an invasive fungal infection should be suspected if they develop a serious systemic illness. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections, if feasible.

Tuberculosis
There have been reports of tuberculosis in patients receiving golimumab. It should be noted that in the majority of these reports, tuberculosis was extrapulmonary presenting as either local or disseminated disease.

Before starting treatment with golimumab, 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 or blood 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, golimumab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of golimumab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of golimumab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of golimumab. Use of anti-tuberculosis therapy should also be considered before the initiation of golimumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Cases of active tuberculosis have occurred in patients treated with golimumab during and after treatment for latent tuberculosis. Patients receiving golimumab should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

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 golimumab treatment.

Hepatitis B virus reactivation
Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including golimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with golimumab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with golimumab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, golimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Malignancies and lymphoproliferative disorders
The potential role of TNF-blocking therapy in the development of malignancies is not known. Based on the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

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

Lymphoma and leukaemia
In the controlled portions of clinical trials of all the TNF-blocking agents including golimumab, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the Simponi Phase IIb and Phase III clinical trials in RA, PsA and AS, the incidence of lymphoma in golimumab-treated patients was higher than expected in the general population. Cases of leukaemia have been reported in patients treated with golimumab. 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.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with other TNF-blocking agents (see section 4.8). This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of cases have occurred in adolescent and young adult males with nearly all on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) for inflammatory bowel disease. The potential risk with the combination of AZA or 6-MP and golimumab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Malignancies other than lymphoma
In the controlled portions of the Simponi Phase IIb and Phase III clinical trials in RA, PsA, AS, and UC, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups.

Colon dysplasia/carcinoma
It is not known if golimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with golimumab, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

In an exploratory clinical trial evaluating the use of golimumab in patients with severe persistent asthma, more malignancies were reported in patients treated with golimumab compared with control patients (see section 4.8). The significance of this finding is unknown.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with an increased risk of malignancy due to heavy smoking.

Skin cancers
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents, including golimumab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

Congestive heart failure (CHF)
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including golimumab. Some cases had a fatal outcome. In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to CHF have been observed. Golimumab has not been studied in patients with CHF. Golimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and golimumab must be discontinued in patients who develop new or worsening symptoms of heart failure (see section 4.3).

Neurological events
Use of TNF-blocking agents, including golimumab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy. Discontinuation of golimumab should be considered if these disorders develop (see section 4.8).

Surgery
There is limited safety experience of golimumab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on golimumab should be closely monitored for infections, and appropriate actions should be taken.

Immunosuppression
The possibility exists for TNF-blocking agents, including golimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Autoimmune processes
The relative deficiency of TNF_{α} caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with golimumab and is positive for antibodies against double-stranded DNA, treatment with golimumab should be discontinued (see section 4.8).

Haematologic reactions
There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anaemia, and thrombocytopenia in patients receiving TNF-blockers, including golimumab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of golimumab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent administration of TNF-antagonists and anakinra
Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. The combination of golimumab and anakinra is not recommended.

Concurrent administration of TNF-antagonists and abatacept
In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of golimumab and abatacept is not recommended.

Concurrent administration with other biological therapeutics
There is insufficient information regarding the concomitant use of golimumab with other biological therapeutics used to treat the same conditions as golimumab. The concomitant use of golimumab with

these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs
Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Vaccinations/therapeutic infectious agents
Patients treated with golimumab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6). In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g. BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with golimumab.

Allergic reactions
In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following golimumab administration. Some of these reactions occurred after the first administration of golimumab. If an anaphylactic reaction or other serious allergic reactions occur, administration of golimumab should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity
The needle cover on the pre-filled pen or the pre-filled syringe is manufactured from dry natural rubber containing latex, and may cause allergic reactions in individuals sensitive to latex.

Special populations

Elderly (≥ 65 years)
In the Phase III studies in RA, PsA, AS, and UC, no overall differences in adverse events (AEs), serious adverse events (SAEs), and serious infections in patients age 65 or older who received golimumab 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. There were no patients age 45 and over in the nr-Axial SpA study.

Renal and hepatic impairment
Specific studies of golimumab have not been conducted in patients with renal or hepatic impairment. Golimumab should be used with caution in subjects with impaired hepatic function (see section 4.2).

Paediatrics
Vaccinations
If possible, it is recommended that prior to initiating golimumab therapy, paediatric patients be brought up to date with all immunisations in agreement with current immunisation guidelines (see Vaccinations/ therapeutic infectious agents above).

Excipients with known effect
Sorbitol
Simponi contains sorbitol (E420). In patients with rare hereditary problems of fructose intolerance, the additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account (see section 2).

Polysorbate 80
Simponi contains 0.15 mg of polysorbate 80 (E433) in each pre-filled syringe. Polysorbates may cause allergic reactions (see section 2).

Potential for medication errors
Simponi is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in the posology (see section 4.2). Care should be taken to provide the right strength to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with other biological therapeutics
The combination of golimumab with other biological therapeutics used to treat the same conditions as golimumab, including anakinra and abatacept is not recommended (see section 4.4).

Live vaccines/therapeutic infectious agents
Live vaccines should not be given concurrently with golimumab (see sections 4.4 and 4.6).

Therapeutic infectious agents should not be given concurrently with golimumab (see section 4.4).

Methotrexate
Although concomitant use of MTX results in higher steady-state trough concentrations of golimumab in patients with RA, PsA or AS, the data do not suggest the need for dose adjustment of either golimumab or MTX (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last golimumab treatment.

Pregnancy
There is a moderate amount (approximately 400) of prospectively collected pregnancies exposed to golimumab resulting in live birth with known outcomes, including 220 pregnancies exposed during the first trimester. In a population-based study from Northern Europe including 131 pregnancies (and 134 infants), there were 6/134 (4.5%) events of major congenital anomalies following *in utero* exposure to Simponi vs 599/10,823 (5.5%) events for non-biologic systemic therapy compared to 4.6% in the general population of the study. Confounder-adjusted odds ratios were OR 0.79 (95% CI 0.35-1.81) for Simponi vs. non-biologic systemic therapy and OR 0.95 (95% CI 0.42-2.16) for Simponi vs. the general population, respectively.

Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The available clinical experience is limited. Golimumab should only be used during pregnancy if clearly needed.

Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see sections 4.4 and 4.5).

Breast-feeding
It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Golimumab was shown to pass over to breast milk in monkeys, and because human immunoglobulins are excreted in milk, women must not breast feed during and for at least 6 months after golimumab treatment.

Fertility
No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, showed no relevant effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Simponi has minor influence on the ability to drive and use machines. Dizziness may however occur following administration of Simponi (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
In the controlled period of the pivotal trials in RA, PsA, AS, nr-Axial SpA, and UC, upper respiratory tract infection was the most common adverse reaction (AR) reported in 12.6% of golimumab-treated patients compared with 11.0% of control patients. The most serious ARs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome), haematologic reactions, serious systemic hypersensitivity (including anaphylactic reaction), vasculitis, lymphoma and leukaemia (see section 4.4).

Tabulated list of adverse reactions
ARs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed in Table 2. Within the designated system organ classes, the ARs are listed under headings of frequency and using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2
Tabulated list of ARs

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)
Common:	Bacterial infections (such as cellulitis), lower respiratory tract infection (such as pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess
Uncommon:	Sepsis including septic shock, pyelonephritis
Rare:	Tuberculosis, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), hepatitis B reactivation, bacterial arthritis, infective bursitis
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia, melanoma, Merkel cell carcinoma
Not known:	Hepatosplenic T-cell lymphoma*, Kaposi's sarcoma

Blood and lymphatic system disorders		
	Common:	Leukopenia (including neutropenia), anaemia
	Uncommon:	Thrombocytopenia, pancytopenia
	Rare:	Aplastic anaemia, agranulocytosis
Immune system disorders		
	Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
	Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis
Endocrine disorders		
	Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders		
	Uncommon:	Blood glucose increased, lipids increased
Psychiatric disorders		
	Common:	Depression, insomnia
Nervous system disorders		
	Common:	Dizziness, headache, paraesthesia
	Uncommon:	Balance disorders
	Rare:	Demyelinating disorders (central and peripheral), dysgeusia
Eye disorders		
	Uncommon:	Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritus and irritation)
Cardiac disorders		
	Uncommon:	Arrhythmia, ischaemic coronary artery disorders
	Rare:	Congestive heart failure (new onset or worsening)
Vascular disorders		
	Common:	Hypertension
	Uncommon:	Thrombosis (such as deep venous and aortic), flushing
	Rare:	Raynaud’s phenomenon
Respiratory, thoracic and mediastinal disorders		
	Common:	Asthma and related symptoms (such as wheezing and bronchial hyperactivity)
	Uncommon:	Interstitial lung disease
Gastrointestinal disorders		
	Common:	Dyspepsia, gastrointestinal and abdominal pain, nausea, gastrointestinal inflammatory disorders (such as gastritis and colitis), stomatitis
	Uncommon:	Constipation, gastro-oesophageal reflux disease
Hepatobiliary disorders		
	Common:	Alanine aminotransferase increased, aspartate aminotransferase increased
	Uncommon:	Cholelithiasis, hepatic disorders
Skin and subcutaneous tissue disorders		
	Common:	Pruritus, rash, alopecia, dermatitis
	Uncommon:	Bullous skin reactions, psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria
	Rare:	Lichenoid reactions, skin exfoliation, vasculitis (cutaneous)
	Not known:	Worsening of symptoms of dermatomyositis
Musculoskeletal and connective tissue disorders		
	Rare:	Lupus-like syndrome

Renal and urinary disorders	
Rare:	Bladder disorders, renal disorders
Reproductive system and breast disorders	
Uncommon:	Breast disorders, menstrual disorders
General disorders and administration site conditions	
Common:	Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia), chest discomfort
Rare:	Impaired healing
Injury, poisoning and procedural complications	
Common:	Bone fractures

* Observed with other TNF-blocking agents.

Throughout this section, median duration of follow-up (approximately 4 years) is generally presented for all golimumab use. Where golimumab use is described by dose, the median duration of follow-up varies (approximately 2 years for 50 mg dose, approximately 3 years for 100 mg dose) as patients may have switched between doses.

Description of selected adverse reactions

Infections
In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of golimumab-treated patients (incidence per 100 subject-years: 60.8; 95% CI: 55.0, 67.1) compared with 11.0% of control patients (incidence per 100 subject-years: 54.5; 95% CI: 46.1, 64.0). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 4 years, the incidence per 100 subject-years of upper respiratory tract infections was 34.9 events; 95% CI: 33.8, 36.0 for golimumab treated patients.

In the controlled period of pivotal trials, infections were observed in 23.0% of golimumab-treated patients (incidence per 100 subject-years: 132.0; 95% CI: 123.3, 141.1) compared with 20.2% of control patients (incidence per 100 subject-years: 122.3; 95% CI: 109.5, 136.2). In controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per 100 subject-years of infections was 81.1 events; 95% CI: 79.5, 82.8 for golimumab treated patients.

In the controlled period of RA, PsA, AS, and nr-Axial SpA trials, serious infections were observed in 1.2% of golimumab-treated patients and 1.2% of control-treated patients. The incidence of serious infections per 100 subject-years of follow-up in the controlled period of RA, PsA, AS, and nr-Axial SpA trials was 7.3; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 2.9; 95% CI: 1.2, 6.0 for the golimumab 50 mg group and 3.6; 95% CI: 1.5, 7.0 for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of golimumab-treated patients compared with 1.5% of control-treated patients. Serious infections observed in golimumab-treated patients included tuberculosis, bacterial infections including sepsis and pneumonia, invasive fungal infections and other opportunistic infections. Some of these infections have been fatal. In the controlled and uncontrolled portions of the pivotal trials with a median follow-up of up to 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 4.1; 95% CI: 3.6, 4.5, in patients receiving golimumab 100 mg and 2.5; 95% CI: 2.0, 3.1, in patients receiving golimumab 50 mg.

Malignancies
Lymphoma
The incidence of lymphoma in golimumab-treated patients during the pivotal trials was higher than expected in the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients

receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Lymphoma was diagnosed in 11 subjects (1 in the golimumab 50 mg treatment groups and 10 in the golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.03 (0.00, 0.15) and 0.13 (0.06, 0.24) events for golimumab 50 mg and 100 mg respectively and 0.00 (0.00, 0.57) events for the placebo. The majority of lymphomas occurred in study GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease (see section 4.4).

Malignancies other than lymphoma
In the controlled periods of pivotal trials and through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar to the general population.

In the controlled and uncontrolled periods of pivotal trials with a median follow-up of up to 3 years, non-melanoma skin cancer was diagnosed in 5 placebo-treated, 10 golimumab 50 mg-treated and 31 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.36 (0.26, 0.49) for combined golimumab and 0.87 (0.28, 2.04) for placebo.

In the controlled and uncontrolled period of pivotal trials with a median follow-up of up to 3 years, malignancies besides melanoma, non-melanoma skin cancer and lymphoma were diagnosed in 5 placebo-treated, 21 golimumab 50 mg-treated and 34 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.48 (0.36, 0.62) for combined golimumab and 0.87 (0.28, 2.04) for placebo (see section 4.4).

Cases reported in clinical studies in asthma
In an exploratory clinical study, patients with severe persistent asthma received a golimumab loading dose (150% of the assigned treatment dose) subcutaneously at week 0 followed by golimumab 200 mg, golimumab 100 mg or golimumab 50 mg every 4 weeks subcutaneously through week 52. Eight malignancies in the combined golimumab treatment group (n = 230) and none in the placebo treatment group (n = 79) were reported. Lymphoma was reported in 1 patient, non-melanoma skin cancer in 2 patients, and other malignancies in 5 patients. There was no specific clustering of any type of malignancy.

During the placebo-controlled portion of the study, the incidence (95% CI) of all malignancies per 100 subject-years of follow-up was 3.19 (1.38, 6.28) in the golimumab group. In this study, the incidence (95% CI) per 100 subject-years of follow-up in golimumab-treated subjects was 0.40 (0.01, 2.20) for lymphoma, 0.79 (0.10, 2.86) for non-melanoma skin cancers, and 1.99 (0.64, 4.63) for other malignancies. For placebo subjects, the incidence (95% CI) per 100 subject-years of follow-up of these malignancies was 0.00 (0.00, 2.94). The significance of this finding is unknown.

Neurological events
In the controlled and uncontrolled periods of the pivotal trials with a median follow-up of up to 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg (see section 4.4).

Liver enzyme elevations
In the controlled period of RA and PsA pivotal trials, mild ALT elevations (> 1 and < 3 x upper limit of normal (ULN)) occurred in similar proportions of golimumab and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS and nr-Axial SpA studies, more golimumab-treated patients (26.9%) than control patients (10.6%) had mild ALT elevations. In the controlled and uncontrolled periods of the RA and PsA pivotal trials, with a median follow-up of approximately 5 years, the incidence of mild ALT elevations was similar in golimumab-treated and control patients in RA and PsA studies. In the controlled period of the UC pivotal trials of golimumab induction, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of golimumab-treated and control patients (8.0% to 6.9%, respectively). In controlled and uncontrolled periods of the

UC pivotal trials with a median follow-up of approximately 2 years, the proportion of patients with mild ALT elevations was 24.7% in patients receiving golimumab during the maintenance portion of the UC study.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5 x ULN were uncommon and seen in more golimumab-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. In the controlled and uncontrolled periods of RA, PsA and AS pivotal trials, with a median follow-up of 5 years, the incidence of ALT elevations ≥ 5 x ULN was similar in both golimumab-treated and control patients. In general these elevations were asymptomatic and the abnormalities decreased or resolved with either continuation or discontinuation of golimumab or modification of concomitant medicinal products. No cases were reported in the controlled and uncontrolled periods of the nr-Axial SpA study (up to 1 year). In the controlled periods of the pivotal UC trials, of golimumab induction, ALT elevations ≥ 5 x ULN occurred in similar proportions of golimumab-treated patients compared to placebo-treated patients (0.3% to 1.0%, respectively). In the controlled and uncontrolled periods of the pivotal UC trials with a median follow-up of approximately 2 years, the proportion of patients with ALT elevations ≥ 5 x ULN was 0.8% in patients receiving golimumab during the maintenance portion of the UC study.

Within the RA, PsA, AS, and nr-Axial SpA pivotal trials, one patient in an RA trial with pre-existing liver abnormalities and confounding medicinal products treated with golimumab developed non-infectious fatal hepatitis with jaundice. The role of golimumab as a contributing or aggravation factor cannot be excluded.

Injection site reactions
In the controlled periods of pivotal trials, 5.4% of golimumab-treated patients had injection site reactions compared with 2.0% in control patients. The presence of antibodies to golimumab may increase the risk of injection site reactions. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

In controlled Phase IIb and/or III trials in RA, PsA, AS, nr-Axial SpA, severe persistent asthma, and Phase II/III trials in UC, no patients treated with golimumab developed anaphylactic reactions.

Autoimmune antibodies
In the controlled and uncontrolled periods of pivotal trials through 1 year of follow-up, 3.5% of golimumab-treated patients and 2.3% of control patients were newly ANA-positive (at titres of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients anti-dsDNA negative at baseline was 1.1%.

Paediatric population
Ulcerative colitis
The safety of golimumab has been studied in a Phase III study of 69 patients from 4 to 17 years of age with moderately to severely active ulcerative colitis. In this study, adverse reactions observed were consistent with the established safety profile of golimumab in adult patients with UC.

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

Single doses up to 10 mg/kg intravenously have been administered in a clinical study without dose-limiting toxicity. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors, ATC code: L04AB06

Mechanism of action
Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors.

Pharmacodynamic effects
The binding of human TNF by golimumab was shown to neutralise TNF-α-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. *In vitro*, TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab.

Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with Simponi resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix-metalloproteinase (MMP)-3 and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNF-α were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients. These changes were observed at the first assessment (week 4) after the initial Simponi administration and were generally maintained through week 24.

Clinical efficacy

Adult rheumatoid arthritis
The efficacy of Simponi was demonstrated in three multi-centre, randomised, double-blind, placebo-controlled studies in over 1500 patients ≥ 18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening. Patients had at least 4 swollen and 4 tender joints. Simponi or placebo were subcutaneously administered every 4 weeks.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. Patients receiving placebo + MTX were switched to Simponi 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

GO-AFTER evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomised to receive placebo, Simponi 50 mg, or Simponi 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Simponi 50 mg + MTX.

In GO-FORWARD, the (co-) primary endpoints were the percentage of patients achieving an ACR 20 response at week 14 and the improvement from baseline in Health Assessment Questionnaire (HAQ) at week 24. In GO-AFTER, the primary endpoint was the percentage of patients achieving an ACR 20 response at week 14. In GO-BEFORE, the co-primary endpoints were the percentage of patients achieving ACR 50 response at week 24 and the change from baseline in the van der Heijde-modified Sharp (vdH-S) score at week 52. In addition to the primary endpoint(s), additional assessments of the impact of Simponi treatment on the signs and symptoms of arthritis, radiographic response, physical function and health-related quality of life were performed.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens with concomitant MTX, through week 104 in GO-FORWARD and GO-BEFORE and through week 24 in GO-AFTER. In each of the RA studies by study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms

Key ACR results for the Simponi 50 mg dose at weeks 14, 24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 3 and are described below. Responses were observed at the first assessment (week 4) after the initial Simponi administration.

In GO-FORWARD, among 89 subjects randomised to Simponi 50 mg + MTX, 48 were still on this treatment at week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving Simponi than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 3
Key efficacy outcomes from the controlled portions of GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	Simponi 50 mg + MTX	Placebo	Simponi 50 mg	Placebo + MTX	Simponi 50 mg + MTX
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA
Week 24	28%	60%*	16%	31% p = 0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p = 0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p = 0.008	2%	10% p = 0.005	NA	NA
Week 24	5%	20%*	2%	9% p = 0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.
* $p \leq 0.001$
NA: Not Applicable

In GO-BEFORE the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Simponi 50 and 100 mg + MTX groups vs MTX alone for ACR50) was not statistically significant at week 24 ($p = 0.053$). At week 52 in the overall population, the percentage of patients in the Simponi 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 3). Additional analyses were performed in subsets representative of the indicated population of patients with severe, active and progressive RA. A generally greater effect of Simponi 50 mg + MTX versus MTX alone was demonstrated in the indicated population compared with the overall population.

In GO-FORWARD and GO-AFTER, clinically meaningful and statistically significant responses in Disease Activity Scale (DAS)28 were observed at each prespecified time point, at week 14 and at week 24 ($p \leq 0.001$). Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 responses were similar from week 104 through week 256.

In GO-BEFORE, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At week 52, 15% of patients in the Simponi 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group ($p = 0.018$). Among 159 subjects randomised to Simponi 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response were observed from week 104 through week 256.

Radiographic response
In GO-BEFORE the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Simponi 50 mg dose at week 52 are presented in Table 4.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the Simponi treatment group than in the control group ($p = 0.003$). The radiographic effects observed at week 52 were maintained through week 104. Among patients remaining in the study and treated with Simponi, radiographic effects were similar from week 104 through week 256.

Table 4
Radiographic mean (SD) changes from baseline in total vdH-S score at week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Simponi 50 mg + MTX**
n[a]	**160**	**159**
Total Score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion Score		
Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.7 (2.8)	0.5 (2.1)
JSN Score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)**

[a] n reflects randomised patients
[*] p = 0.015
[**] p = 0.044

Physical function and health-related quality of life
Physical function and disability were assessed as a separate endpoint in GO-FORWARD and GO-AFTER using the disability index of the HAQ DI. In these studies, Simponi demonstrated clinically meaningful and statistically significant improvement in HAQ DI from baseline versus control at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement in HAQ DI was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement in HAQ DI was similar from week 104 through week 256.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with Simponi versus placebo at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement of the SF-36 physical component was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement of the SF-36 physical component was similar from week 104 through week 256. In GO-FORWARD and GO-AFTER, statistically significant improvements were observed in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F).

Adult psoriatic arthritis
The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months and had at least mild psoriatic disease. Patients with each sub-type of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). Previous treatment with an anti-TNF agent was not allowed. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg, or Simponi 100 mg. Patients receiving placebo were switched to Simponi 50 mg after week 24. Patients entered an open label long-term extension at week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at week 14 and change from baseline in total PsA modified vdH-S score at week 24.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 104. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms
Key results for the 50 mg dose at weeks 14 and 24 are shown in Table 5 and described below.

Table 5
Key efficacy outcomes from GO-REVEAL

	Placebo	Simponi 50 mg*
n[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	**9%**	**51%**
Week 24	12%	52%

ACR 50		
Week 14	2%	30%
Week 24	4%	32%
ACR 70		
Week 14	1%	12%
Week 24	1%	19%
PASI[b] 75[c]		
Week 14	3%	40%
Week 24	1%	56%

* $p < 0.05$ for all comparisons;

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

[b] *Psoriasis Area and Severity Index*

[c] Based on the subset of patients with ≥ 3% BSA involvement at baseline, 79 patients (69.9%) in the placebo group and 109 (74.3%) in the Simponi 50 mg group.

Responses were observed at the first assessment (week 4) after the initial Simponi administration. Similar ACR 20 responses at week 14 were observed in patients with polyarticular arthritis with no rheumatoid nodules and asymmetric peripheral arthritis PsA subtypes. The number of patients with other PsA subtypes was too small to allow meaningful assessment. Responses observed in the Simponi treated groups were similar in patients receiving and not receiving concomitant MTX. Among 146 patients randomised to Simponi 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 ($p < 0.05$).

At week 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Simponi-treated patients. Simponi treatment resulted in significant improvement in physical function as assessed by HAQ DI, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36. Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 and HAQ DI responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 and HAQ DI responses were similar from week 104 through week 256.

Radiographic response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the vdH-S score, modified for PsA by addition of hand distal interphalangeal (DIP) joints.

Simponi 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean ± SD score was 0.27 ± 1.3 in the placebo group compared with -0.16 ± 1.3 in the Simponi group; $p = 0.011$). Out of 146 patients who were randomised to Simponi 50 mg, 52 week X-ray data were available for 126 patients, of whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline. Among patients remaining in the study and treated with Simponi, similar rates of patients showed no progression from baseline from week 104 through week 256.

Adult axial spondyloarthritis

Adult ankylosing spondylitis

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and a VAS for total back pain of ≥ 4, on a scale of 0 to 10 cm). Patients enrolled in this study had active disease despite current or previous NSAID or DMARD therapy and had not previously been treated with anti-TNF therapy. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were

randomly assigned to placebo, Simponi 50 mg and Simponi 100 mg and were allowed to continue concomitant DMARD therapy (MTX, SSZ and/or HCQ). The primary endpoint was the percentage of patients achieving Ankylosing Spondylitis Assessment Study Group (ASAS) 20 response at week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

Key results for the 50 mg dose are shown in Table 6 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 24. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Table 6
Key efficacy outcomes from GO-RAISE

	Placebo	Simponi 50 mg*
n[a]	78	138
Responders, % of patients		
ASAS 20		
Week 14	**22%**	**59%**
Week 24	23%	56%
ASAS 40		
Week 14	15%	45%
Week 24	15%	44%
ASAS 5/6		
Week 14	8%	50%
Week 24	13%	49%

* $p \leq 0.001$ for all comparisons

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

Among patients remaining in the study and treated with Simponi, the proportion of patients with an ASAS 20 and ASAS 40 response were similar from week 24 through week 256.

Statistically significant responses in BASDAI 50, 70 and 90 ($p \leq 0.017$) were also seen at weeks 14 and 24. Improvements in key measures of disease activity were observed at the first assessment (week 4) after the initial Simponi administration and were maintained through week 24. Among patients remaining in the study and treated with Simponi, similar rates of change from baseline in BASDAI were observed from week 24 through week 256. Consistent efficacy was seen in patients regardless of use of DMARDs (MTX, sulfasalazine and/or hydroxychloroquine), HLA-B27 antigen status or baseline CRP levels as assessed by ASAS 20 responses at week 14.

Simponi treatment resulted in significant improvements in physical function as assessed by changes from baseline in BASFI at weeks 14 and 24. Health-related quality of life as measured by the physical component score of the SF-36 was also improved significantly at weeks 14 and 24. Among patients remaining in the study and treated with Simponi, improvements in physical function and health-related quality of life were similar from week 24 through week 256.

Adult non-radiographic axial spondyloarthritis

GO-AHEAD

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-AHEAD) in 197 adult patients with severe active nr-Axial SpA (defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS). Patients enrolled in this study had active disease (defined as a BASDAI ≥ 4 and a Visual Analogue Scale (VAS) for total back pain of ≥ 4, each on a scale of 0-10 cm) despite current or previous NSAID therapy and had not previously been treated with any biological agents including anti-TNF therapy. Patients were randomly assigned to placebo or Simponi 50 mg administered subcutaneously every 4 weeks. At week 16, patients entered an open label period

in which all patients received Simponi 50 mg administered subcutaneously every 4 weeks through week 48 with efficacy assessments performed through week 52 and safety follow-up through week 60. Approximately 93% of patients who were receiving Simponi at the beginning of the open-label extension (week 16) remained on treatment through the end of the study (week 52). Analyses were performed on both the All Treated (AT, N = 197) and Objective Signs of Inflammation (OSI, N = 158, defined by elevated CRP and/or evidence of sacroiliitis on MRI at baseline) populations. Placebo-controlled efficacy data were collected and analysed through week 16. The primary endpoint was the proportion of patients achieving ASAS 20 response at week 16. Key results are shown in Table 7 and described below.

Table 7
Key efficacy outcomes from GO-AHEAD at week 16

Improvements in signs and symptoms				
	All treated population (AT)		Objective signs of inflammation population (OSI)	
	Placebo	Simponi 50 mg	Placebo	Simponi 50 mg
n[a]	100	97	80	78
Responders, % of patients				
ASAS 20	40%	71%**	38%	77%**
ASAS 40	23%	57%**	23%	60%**
ASAS 5/6	23%	54%**	23%	63%**
ASAS Partial Remission	18%	33%*	19%	35%*
ASDAS-C[b] < 1.3	13%	33%*	16%	35%*
BASDAI 50	30%	58%**	29%	59%**
Inhibition of inflammation in sacroiliac (SI) joints as measured by MRI				
	Placebo	Simponi 50 mg	Placebo	Simponi 50 mg
n[c]	87	74	69	61
Mean change in SPARCC[d] MRI sacroiliac joint score	-0.9	-5.3**	-1.2	-6.4**

[a] n reflects randomised and treated patients

[b] Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (AT-Placebo, N = 90; AT-Simponi 50 mg, N = 88; OSI-Placebo, N = 71; OSI-Simponi 50 mg, N = 71)

[c] n reflects number of patients with baseline and week 16 MRI data

[d] SPARCC (Spondyloarthritis Research Consortium of Canada)

** $p < 0.0001$ for Simponi *vs* placebo comparisons

* $p < 0.05$ for Simponi *vs* placebo comparisons

Statistically significant improvements in signs and symptoms of severe active nr-Axial SpA were demonstrated in patients treated with Simponi 50 mg compared to placebo at week 16 (Table 6). Improvements were observed at the first assessment (week 4) after the initial Simponi administration. SPARCC score as measured by MRI showed statistically significant reductions in SI joint inflammation at week 16 in patients treated with Simponi 50 mg compared to placebo (Table 6). Pain as assessed by the Total Back Pain and Nocturnal Back Pain VAS, and disease activity as measured by ASDAS-C also showed statistically significant improvement from baseline to week 16 in patients treated with Simponi 50 mg compared to placebo ($p < 0.0001$).

Statistically significant improvements in spinal mobility as assessed by BASMI (Bath Ankylosing Spondylitis Metrology Index) and in physical function as assessed by the BASFI were demonstrated in Simponi 50 mg-treated patients as compared to placebo-treated patients ($p < 0.0001$). Patients treated with Simponi experienced significantly more improvements in health-related quality of life as assessed by ASQoL, EQ-5D, and physical and mental components of SF-36, and experienced significantly more improvements in productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI questionnaire than patients receiving placebo.

For all of the endpoints described above, statistically significant results were also demonstrated in the OSI population at week 16.

In both the AT and OSI populations, the improvements in signs and symptoms, spinal mobility, physical function, quality of life, and productivity observed at week 16 among patients treated with Simponi 50 mg continued in those remaining in the study at week 52.

GO-BACK

The efficacy and safety of continued golimumab treatment (full or reduced dosing frequency) compared with treatment withdrawal was assessed in adult patients (18-45 years of age) with active nr-axSpA who demonstrated sustained remission during 10 months of monthly treatment with open-label Simponi (GO-BACK). Eligible patients (who achieved a clinical response by Month 4 and an inactive disease status (ASDAS < 1.3) at both Months 7 and 10) entering the double-blind withdrawal phase were randomised to continued monthly treatment with Simponi (full-treatment regimen, N = 63), every 2-month treatment with Simponi (reduced treatment regimen, N = 63) or monthly placebo treatment (treatment withdrawal, N = 62) for up to approximately 12 months.

The primary efficacy endpoint was the proportion of patients without a flare of disease activity. Patients who experienced a flare, i.e., had an ASDAS collected at 2 consecutive assessments that both showed either an absolute score of ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (end of open-label period), reinitiated monthly Simponi in an open-label retreatment phase to characterise clinical response.

Clinical response after double-blind treatment withdrawal
Among the 188 patients with inactive disease who received at least one dose of double-blind treatment, a significantly ($p < 0.001$) greater proportion of patients did not experience a disease flare when continuing Simponi with either the full-treatment (84.1%), or reduced treatment (68.3%) regimens compared with treatment withdrawal (33.9%) (Table 8).

Table 8
Analysis of the proportion of participants without a flare[a]
Full analysis set population (Period 2 – Double-blind)

			Difference in % vs Placebo	
Treatment	**n/N**	**%**	**Estimate (95% CI)[b]**	**p-Value[b]**
GLM SC QMT	53/63	84.1	50.2 (34.1, 63.6)	< 0.001
GLM SC Q2MT	43/63	68.3	34.4 (17.0, 49.7)	< 0.001
Placebo	21/62	33.9		

Full Analysis Set includes all randomised participants who attained inactive disease in period 1 and received at least one dose of blinded study treatment.

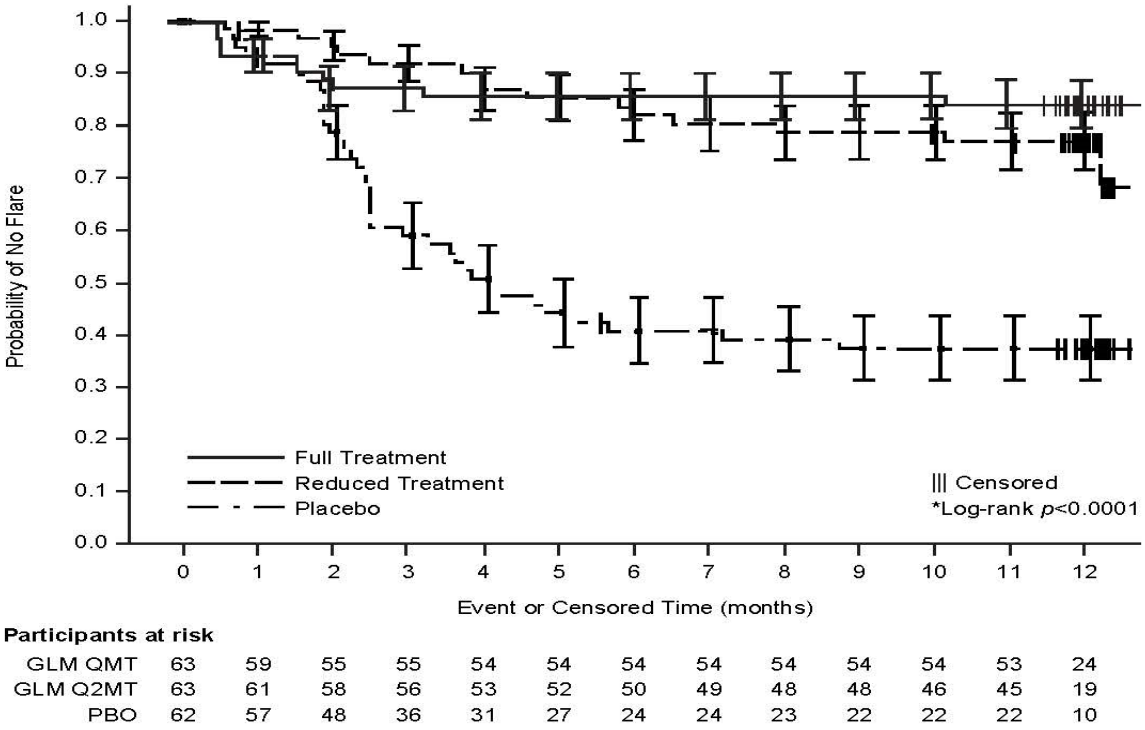
[a] Defined as ASDAS at 2 consecutive visits that both show either absolute score ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23).

[b] Type I error rate over the multiple treatment comparisons (GLM SC QMT vs Placebo and GLM SC Q2MT vs Placebo) was controlled using a sequential (step-down) testing procedure. Derived based on the stratified Miettinen and Nurminen method with CRP level (> 6 mg/L or ≤ 6 mg/L) as stratification factor.

Participants who discontinued period 2 prematurely and prior to a 'flare' will be counted as having a 'flare'.
N = Total number of participants; n = number of participants without a flare; GLM = golimumab; SC = subcutaneous, QMT = monthly dosing; Q2MT = every other month dosing.

The difference in time-to-first flare between the treatment withdrawal group and either of the Simponi Treatment groups is shown in Figure 1 (log-rank $p < 0.0001$ for each comparison). In the placebo group, flares started approximately 2 months after Simponi was withdrawn, with the majority of flares occurring within 4 months of treatment withdrawal (Figure 1).

Figure 1: Kaplan-Meier Analysis of Time-to-First Flare



Participants at risk

GLM QMT	63	59	55	55	54	54	54	54	54	54	54	53	24
GLM Q2MT	63	61	58	56	53	52	50	49	48	48	46	45	19
PBO	62	57	48	36	31	27	24	24	23	22	22	22	10

*Endpoint not adjusted for multiplicity. Stratified by CRP level (> 6 mg/L or ≤ 6 mg/L). Flare was defined as an ASDAS at 2 consecutive visits that both showed either an absolute score of ≥ 2.1 or a post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23). Participants who did not flare were censored at the time of discontinuation or Month 13 of Period 2 double-blind treatment. Start of Period 2 represents Day 1 of the Kaplan-Meier analysis for the full analysis set.

Clinical response to retreatment for a disease flare
Clinical response was defined as a BASDAI improvement of ≥ 2 or ≥ 50% relative to the mean of the 2 consecutive BASDAI scores ascribed to the disease flare. Of the 53 participants in the reduced dosing or treatment withdrawal regimens who had a confirmed disease flare, 51 (96.2%) attained a clinical response to Simponi within the first 3 months of retreatment, although fewer patients (71.7%) were able to sustain it for all 3 months.

Adult ulcerative colitis
The efficacy of Simponi was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients.

The induction study (PURSUIT-Induction) evaluated patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) who had an inadequate response to or failed to tolerate conventional therapies, or were corticosteroid dependent. In the dose confirming portion of the study, 761 patients were randomised to receive either 400 mg Simponi SC at week 0 and 200 mg at week 2, 200 mg Simponi SC at week 0 and 100 mg at week 2, or placebo SC at weeks 0 and 2. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. The efficacy of Simponi through week 6 was assessed in this study.

The results of the maintenance study (PURSUIT-Maintenance) were based on evaluation of 456 patients who achieved clinical response from previous induction with Simponi. Patients were randomised to receive Simponi 50 mg, Simponi 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, and/or immunomodulatory agents were permitted. Corticosteroids were to be tapered at the start of the maintenance study. The efficacy of Simponi through week 54 was assessed in this study. Patients who completed the maintenance study through week 54 continued treatment in a study extension, with efficacy evaluated through week 216. Efficacy evaluation in the study extension was based on changes in corticosteroid use, Physician's Global Assessment (PGA) of disease activity, and improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire (IBDQ).

Table 9
Key efficacy outcomes from PURSUIT - Induction and PURSUIT - Maintenance

PURSUIT-Induction			
	Placebo N = 251	**Simponi 200/100 mg** N = 253	
Percentage of patients			
Patients in clinical response at week 6[a]	30%	51%**	
Patients in clinical remission at week 6[b]	6%	18%**	
Patients with mucosal healing at week 6[c]	29%	42%*	
PURSUIT-Maintenance			
	Placebo[d] N = 154	**Simponi 50 mg** N = 151	**Simponi 100 mg** N = 151
Percentage of patients			
Maintenance of response (Patients in clinical response through week 54)[e]	31%	47%*	50%**
Sustained remission (Patients in clinical remission at both week 30 and week 54)[f]	16%	23%[g]	28%*

N = number of patients

** $p \leq 0.001$

* $p \leq 0.01$

[a] defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

[b] Defined as a Mayo score ≤ 2 points, with no individual subscore > 1

[c] Defined as 0 or 1 on the endoscopy subscore of the Mayo score.

[d] Simponi induction only.

[e] Patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). Therefore, a patient who maintained response was in a state of continuous clinical response at each evaluation through week 54.

[f] A patient had to be in remission at both weeks 30 and 54 (without demonstrating a loss of response at any time point through week 54) to achieve durable remission.

[g] In patients weighing less than 80 kg, a greater proportion of patients who received 50 mg maintenance therapy showed sustained clinical remission compared with those who received placebo.

More Simponi-treated patients demonstrated sustained mucosal healing (patients with mucosal healing at both week 30 and week 54) in the 50 mg group (42%, nominal $p < 0.05$) and 100 mg group (42%, $p < 0.005$) compared with patients in the placebo group (27%).

Among the 54% of patients (247/456) who were receiving concomitant corticosteroids at the start of PURSUIT-Maintenance, the proportion of patients who maintained clinical response through week 54 and were not receiving concomitant corticosteroids at week 54 was greater in the 50 mg group (38%, 30/78) and 100 mg group (30%, 25/82) compared with the placebo group (21%, 18/87). The proportion of patients who eliminated corticosteroids by week 54 was greater in the 50 mg group (41%, 32/78) and 100 mg group (33%, 27/82) compared with the placebo group (22%, 19/87). Among patients who entered the study extension, the proportion of subjects who remained corticosteroid free was generally maintained through week 216.

Patients who did not achieve clinical response at week 6 in the PURSUIT-Induction studies were dosed Simponi 100 mg every 4 weeks in the PURSUIT-Maintenance study. At week 14, 28% of these patients achieved response defined by partial Mayo score (decreased by ≥ 3 points compared with start of induction). At week 54, the clinical outcomes observed in these patients were similar to the clinical outcomes reported for the patients achieving clinical response at week 6.

At week 6, Simponi significantly improved quality of life as measured by change from baseline in a disease specific measure, IBDQ (inflammatory bowel disease questionnaire). Among patients who

received Simponi maintenance treatment, the improvement in quality of life as measured by IBDQ was maintained through week 54.

Approximately 63% of patients who were receiving Simponi at the beginning of the study extension (week 56), remained on treatment through the end of the study (last golimumab administration at week 212).

Paediatric population
Paediatric ulcerative colitis
The safety and efficacy of Simponi was evaluated in a Phase III multi-centre, open-label, study (PURSUIT 2) designed to enroll children 2 to 17 years of age with moderately to severely active UC defined as a baseline full Mayo score of 6 through 12, inclusive, with an endoscopy subscore of ≥ 2. Children with prior exposure to anti-TNF-α agents were ineligible for participation. The majority of the 69 participants (97.1%) were receiving UC-related medications (corticosteroids, immunomodulators, and/or 5-ASA); 52.2% of participants were receiving corticosteroids, and 88.4% were receiving oral 5-ASA. The mean age of participants was 13.4 years (range 4 to 17). 53.6% (37) of participants were female. The mean weight was 52.4 kg (range 16 to 107). Baseline disease characteristics for the overall golimumab population were representative of paediatric patients with moderately to severely active UC.

In the Induction Phase (week 0 to week 6), children received body weight-based golimumab SC, at weeks 0 and 2. Children with body weight ≥ 45 kg received fixed induction doses of 200 mg SC at week 0 and 100 mg at week 2. Children with body weight < 45 kg received body-surface area-adjusted induction doses of 120 mg/m^2 SC (up to a maximum of 200 mg) at week 0 and 60 mg/m^2 SC (up to a maximum of 100 mg) at week 2. At week 6, children were evaluated for efficacy and safety.

In the Maintenance Phase (week 6 through week 54), children in clinical response to golimumab (a decrease from baseline in the full Mayo score of ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1 using the local read for the endoscopy subscore) continued to receive SC golimumab 100 mg (children weighing ≥ 45 kg) or 60 mg/m^2 (children weighing < 45 kg) every 4 weeks through week 50. For children with no clinical response at week 6, additional doses at week 6 and week 10 could have been given, followed by a response assessment at week 14 to determine if the children continued with golimumab every 4 weeks through week 50. Of the 41 children who entered the maintenance phase, 39 children remained in the study at week 54 (had a full Mayo score efficacy determination).

The primary endpoint of clinical remission as measured by the Mayo score was defined as a Mayo score ≤ 2 points, with no individual subscore > 1 (based on Mayo endoscopy subscore assigned by the local endoscopist). Overall, 22 (31.9%) of children showed clinical remission at week 6. At week 54, 31.7% of week 6 clinical responders were in clinical remission.

Table 10
Key efficacy outcomes from PURSUIT 2 – Induction and PURSUIT 2 - Maintenance

PURSUIT 2 - Induction	
Primary Endpoint	**Simponi N=69**
Subjects in clinical remission as assessed by the Mayo score at week 6[a]	22 (31.9%)
Major Secondary Endpoints	
Subjects in clinical response at week 6[b]	39 (56.5%)
Subjects with endoscopic healing at week 6[c]	28 (40.6%)
PURSUIT 2 – Maintenance	
Major Secondary Endpoints	**Simponi N=41**
Subjects in clinical remission at week 54 as assessed by the Mayo score[a,e]	13 (31.7%)
Subjects with endoscopic healing at week 54[c]	15 (36.6%)

Subjects in clinical remission at week 54 as assessed by the Mayo score, for participants who are in clinical remission at Week 6[a,d,e]	12 (54.5%)

N = number of patients

[a] Clinical remission is defined as a Mayo score ≤2 points, with no individual subscore >1.

[b] Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

[c] Endoscopic healing is defined as an endoscopy subscore of 0 or 1 based on local endoscopy.

[d] Denominator is subjects who were in clinical remission at Week 6.

[e] Subjects who had a missing endoscopy score at Week 54 were considered not to be in clinical remission.

Immunogenicity

Across the Phase III RA, PsA and AS studies through week 52, antibodies to golimumab were detected in 5% (105/2062) of golimumab treated patients and, where tested, nearly all antibodies were neutralising *in vitro*. Similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without MTX (approximately 3% [41/1235] versus 8% [64/827], respectively).

In nr-Axial SpA, antibodies to golimumab were detected in 7% (14/193) of golimumab treated patients through week 52.

In the Phase II and III UC studies through week 54, antibodies to golimumab were detected in 3% (26/946) of golimumab treated patients. Sixty-eight percent (21/31) of antibody-positive patients had neutralising antibodies *in vitro*. Treatment with concomitant immunomodulators (azathioprine, 6-mercaptopurine and MTX) resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without immunomodulators (1% (4/308) versus 3% (22/638), respectively). Of patients that continued in the study extension and had evaluable samples through week 228, antibodies to golimumab were detected in 4% (23/604) of golimumab treated patients. Eighty-two percent (18/22) of antibody-positive patients had neutralising antibodies *in vitro*.

The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.8). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

Because immunogenicity analyses are product- and assay-specific, comparison of antibody rates with those from other products is not appropriate.

In the Phase III paediatric UC trial, 22% (15/69) of Simponi-treated patients were positive for antibodies to golimumab through the final safety visit using the drug-tolerant EIA method. Most patients with antibodies had low titres. The incidence of antibodies to golimumab was comparable between paediatric and adult patients with UC. UC patients who developed antibodies to golimumab, generally had lower trough steady-state serum concentrations of golimumab.

5.2 Pharmacokinetic properties

Absorption

Following a single subcutaneous administration of golimumab to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A subcutaneous injection of 50 mg golimumab to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/mL.

Following a single subcutaneous injection of 100 mg, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since golimumab exhibited approximately dose proportional PK following a subcutaneous administration, the absolute bioavailability of a golimumab 50 mg or 200 mg dose is expected to be similar.

Distribution
Following a single IV administration, the mean volume of distribution was 115 ± 19 mL/kg.

Elimination
The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg. Terminal half-life value was estimated to be approximately 12 ± 3 days in healthy subjects and similar values were observed in patients with RA, PsA, AS, or UC.

When 50 mg golimumab was administered subcutaneously to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by week 12. With concomitant use of MTX, treatment with 50 mg golimumab subcutaneously every 4 weeks resulted in a mean (± standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 μg/mL in patients with active PsA and approximately 0.8 ± 0.4 μg/mL in patients with AS. Steady-state trough mean serum golimumab concentrations in patients with nr-Axial SpA were similar to those observed in patients with AS following subcutaneous administration of 50 mg golimumab every 4 weeks.

Patients with RA, PsA or AS who did not receive concomitant MTX had approximately 30% lower steady-state trough concentrations of golimumab than those who received golimumab with MTX. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. However, population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

Following induction doses of 200 mg and 100 mg golimumab at week 0 and 2, respectively, and maintenance doses of 50 mg or 100 mg golimumab subcutaneously every 4 weeks thereafter to patients with UC, serum golimumab concentrations reached steady state approximately 14 weeks after the start of therapy. Treatment with 50 mg or 100 mg golimumab subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 0.9 ± 0.5 μg/mL and 1.8 ± 1.1 μg/mL, respectively.

In UC patients treated with 50 mg or 100 mg golimumab subcutaneously every 4 weeks, concomitant use of immunomodulators did not have a substantial effect on steady-state trough levels of golimumab.

Patients who developed antibodies to golimumab generally had low trough steady-state serum concentrations of golimumab (see section 5.1).

Paediatric ulcerative colitis
The pharmacokinetics of golimumab were similar between paediatric and adult patients with ulcerative colitis. Population pharmacokinetics confirmed that the recommended dosing regimen for Simponi resulted in similar or slightly higher serum golimumab exposure in paediatric subjects as compared to adults across the body weight range.

Linearity
Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose. Following a single SC dose in healthy subjects, approximately dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg.

Effect of weight on pharmacokinetics
There was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

No mutagenicity studies, animal fertility studies nor long-term carcinogenic studies have been conducted with golimumab.

In a fertility and general reproductive function study in mouse, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, the number of pregnant mice was reduced. It is not known whether this finding was due to effects on the males and/or the females. In a developmental toxicity study conducted in mice following administration of the same analogous antibody, and in cynomolgus monkeys using golimumab, there was no indication of maternal toxicity, embryotoxicity or teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect it from light.
Simponi may be stored at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 30 days from the date removed from the refrigerator).

Once Simponi has been stored at room temperature, it should not be returned to refrigerated storage. Simponi must be discarded if not used within the 30 days of room temperature storage.

6.5 Nature and contents of container

<u>Simponi 100 mg solution for injection in pre-filled syringe</u>
1 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex). Simponi is available in packs containing 1 pre-filled syringe and multipacks containing 3 (3 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Simponi is supplied in a single use pre-filled syringe. Each pack is provided with instructions for use that fully describe the use of the syringe. After removing the pre-filled syringe from the refrigerator it should be allowed to reach room temperature by waiting for 30 minutes, before injecting Simponi. The syringe should not be shaken.

The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for solutions containing protein. Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

Comprehensive instructions for the preparation and administration of Simponi in a pre-filled syringe are given in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/007 1 pre-filled syringe
EU/1/09/546/008 3 pre-filled syringes

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 October 2009
Date of latest renewal: 19 June 2014

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

Simponi 100 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL pre-filled pen contains 100 mg of golimumab*.

* Human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology.

Excipients with known effect
Each pre-filled pen contains 41 mg sorbitol (E420) per 100 mg dose.

Each pre-filled pen contains 0.15 mg of polysorbate 80 (E433) per 100 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled pen (SmartJect)

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)
Simponi, in combination with methotrexate (MTX), is indicated for:
- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

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

For information regarding the polyarticular juvenile idiopathic arthritis indication, please see the Simponi 50 mg SmPC.

Psoriatic arthritis (PsA)
Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Simponi has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Axial spondyloarthritis
Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)
Simponi is indicated for the treatment of adults with severe, active 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, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)
Simponi is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

4.2 Posology and method of administration

Treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis. Patients treated with Simponi should be given the Patient Card.

Posology

Rheumatoid arthritis
Simponi 50 mg given once a month, on the same date each month.
Simponi should be given concomitantly with MTX.

Psoriatic arthritis, ankylosing spondylitis, or non-radiographic axial spondyloarthritis
Simponi 50 mg given once a month, on the same date each month.

For all of the above indications, available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Patients with body weight greater than 100 kg
For all of the above indications, in patients with RA, PsA, AS, or nr-Axial SpA with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse reactions with the 100 mg dose compared with the 50 mg dose (see section 4.8). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

Ulcerative colitis
Patients with body weight less than 80 kg
Simponi given as an initial dose of 200 mg, followed by 100 mg at week 2. Patients who have an adequate response should receive 50 mg at week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter (see section 5.1).

Patients with body weight greater than or equal to 80 kg
Simponi given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter (see section 5.1).

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Missed dose
If a patient forgets to inject Simponi on the planned date, the forgotten dose should be injected as soon as the patient remembers. Patients should be instructed not to inject a double dose to make up for the forgotten dose.

The next dose should be administered based on the following guidance:
- if the dose is less than 2 weeks late, the patient should inject the forgotten dose and stay on the original schedule.
- if the dose is more than 2 weeks late, the patient should inject the forgotten dose and a new schedule should be established from the date of this injection.

Special populations
Elderly (≥ 65 years)
No dose adjustment is required in the elderly.

Renal and hepatic impairment
Simponi has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of Simponi in patients aged less than 18 for indications other than pJIA and pUC have not been established. No data are available. There is no relevant use of Simponi in children aged less than 2 years in pJIA or pUC. Simponi 100 mg pre-filled pen has not been studied in the paediatric population and is not recommended for use in this population. See section 4.2 of the 50 mg or 100 mg pre-filled syringe or of the 45 mg/0.45 mL pre-filled pen SmPC for posology and method of administration in pUC patients (from 2 years of age and above 15 kg). See section 4.2 of the 50 mg pre-filled syringe, or of the 50 mg or 45 mg/0.45 mL pre-filled pen SmPC for posology and method of administration in patients with pJIA.

Method of administration
Simponi is for subcutaneous use. After proper training in subcutaneous injection technique, patients may self-inject if their physician determines that this is appropriate, with medical follow-up as necessary. Patients should be instructed to inject the full amount of Simponi according to the comprehensive instructions for use provided in the package leaflet. If multiple injections are required, the injections should be administered at different sites on the body. Each pre-filled pen is for single use in a single patient, and should be discarded immediately after use.

For administration instructions, see section 6.6.

4.3 Contraindications

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

Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate or severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections
Patients must be monitored closely for infections including tuberculosis before, during and after treatment with golimumab. Because the elimination of golimumab may take up to 5 months,

monitoring should be continued throughout this period. Further treatment with golimumab must not be given if a patient develops a serious infection or sepsis (see section 4.3).

Golimumab should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of golimumab in patients with a chronic infection or a history of recurrent infection. Patients should be advised of, and avoid exposure to, potential risk factors for infection as appropriate.

Patients taking TNF-blockers are more susceptible to serious infections.
Bacterial (including sepsis and pneumonia), mycobacterial (including TB), invasive fungal and opportunistic infections, including fatalities, have been reported in patients receiving golimumab. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with golimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of golimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of golimumab treatment should be carefully considered before initiation of golimumab therapy. In at-risk patients treated with golimumab, an invasive fungal infection should be suspected if they develop a serious systemic illness. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections, if feasible.

Tuberculosis
There have been reports of tuberculosis in patients receiving golimumab. It should be noted that in the majority of these reports, tuberculosis was extrapulmonary presenting as either local or disseminated disease.

Before starting treatment with golimumab, 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 or blood 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, golimumab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of golimumab therapy should be very carefully considered.

If inactive (‘latent’) tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of golimumab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of golimumab. Use of anti-tuberculosis therapy should also be considered before the initiation of golimumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Cases of active tuberculosis have occurred in patients treated with golimumab during and after treatment for latent tuberculosis. Patients receiving golimumab should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

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 golimumab treatment.

Hepatitis B virus reactivation
Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including golimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with golimumab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with golimumab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, golimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Malignancies and lymphoproliferative disorders
The potential role of TNF-blocking therapy in the development of malignancies is not known. Based on the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

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

Lymphoma and leukaemia
In the controlled portions of clinical trials of all the TNF-blocking agents including golimumab, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the Simponi Phase IIb and Phase III clinical trials in RA, PsA and AS, the incidence of lymphoma in golimumab-treated patients was higher than expected in the general population. Cases of leukaemia have been reported in patients treated with golimumab. 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.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with other TNF-blocking agents (see section 4.8). This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of cases have occurred in adolescent and young adult males with nearly all on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) for inflammatory bowel disease. The potential risk with the combination of AZA or 6-MP and golimumab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Malignancies other than lymphoma
In the controlled portions of the Simponi Phase IIb and Phase III clinical trials in RA, PsA, AS, and UC, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups.

Colon dysplasia/carcinoma
It is not known if golimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with golimumab, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

In an exploratory clinical trial evaluating the use of golimumab in patients with severe persistent asthma, more malignancies were reported in patients treated with golimumab compared with control patients (see section 4.8). The significance of this finding is unknown.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with an increased risk of malignancy due to heavy smoking.

Skin cancers
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents, including golimumab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

Congestive heart failure (CHF)
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including golimumab. Some cases had a fatal outcome. In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to CHF have been observed. Golimumab has not been studied in patients with CHF. Golimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and golimumab must be discontinued in patients who develop new or worsening symptoms of heart failure (see section 4.3).

Neurological events
Use of TNF-blocking agents, including golimumab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy. Discontinuation of golimumab should be considered if these disorders develop (see section 4.8).

Surgery
There is limited safety experience of golimumab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on golimumab should be closely monitored for infections, and appropriate actions should be taken.

Immunosuppression
The possibility exists for TNF-blocking agents, including golimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Autoimmune processes
The relative deficiency of TNF_{α} caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with golimumab and is positive for antibodies against double-stranded DNA, treatment with golimumab should be discontinued (see section 4.8).

Haematologic reactions
There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anaemia, and thrombocytopenia in patients receiving TNF-blockers, including golimumab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of golimumab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent administration of TNF-antagonists and anakinra
Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. The combination of golimumab and anakinra is not recommended.

Concurrent administration of TNF-antagonists and abatacept
In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of golimumab and abatacept is not recommended.

Concurrent administration with other biological therapeutics
There is insufficient information regarding the concomitant use of golimumab with other biological therapeutics used to treat the same conditions as golimumab. The concomitant use of golimumab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs
Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Vaccinations/therapeutic infectious agents
Patients treated with golimumab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6). In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g. BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with golimumab.

Allergic reactions
In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following golimumab administration. Some of these reactions occurred after the first administration of golimumab. If an anaphylactic reaction or other serious allergic

reactions occur, administration of golimumab should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity
The needle cover on the pre-filled pen or the pre-filled syringe is manufactured from dry natural rubber containing latex, and may cause allergic reactions in individuals sensitive to latex.

Special populations

Elderly (≥ 65 years)
In the Phase III studies in RA, PsA, AS, and UC, no overall differences in adverse events (AEs), serious adverse events (SAEs), and serious infections in patients age 65 or older who received golimumab 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. There were no patients age 45 and over in the nr-Axial SpA study.

Renal and hepatic impairment
Specific studies of golimumab have not been conducted in patients with renal or hepatic impairment. Golimumab should be used with caution in subjects with impaired hepatic function (see section 4.2).

Excipients with known effect
Sorbitol
Simponi contains sorbitol (E420). In patients with rare hereditary problems of fructose intolerance, the additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account (see section 2).

Polysorbate 80
Simponi contains 0.15 mg of polysorbate 80 (E433) in each pre-filled pen. Polysorbates may cause allergic reactions (see section 2).

Potential for medication errors
Simponi is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in the posology (see section 4.2). Care should be taken to provide the right strength to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with other biological therapeutics
The combination of golimumab with other biological therapeutics used to treat the same conditions as golimumab, including anakinra and abatacept is not recommended (see section 4.4).

Live vaccines/therapeutic infectious agents
Live vaccines should not be given concurrently with golimumab (see sections 4.4 and 4.6).

Therapeutic infectious agents should not be given concurrently with golimumab (see section 4.4).

Methotrexate
Although concomitant use of MTX results in higher steady-state trough concentrations of golimumab in patients with RA, PsA or AS, the data do not suggest the need for dose adjustment of either golimumab or MTX (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last golimumab treatment.

Pregnancy
There is a moderate amount (approximately 400) of prospectively collected pregnancies exposed to golimumab resulting in live birth with known outcomes, including 220 pregnancies exposed during the first trimester. In a population-based study from Northern Europe including 131 pregnancies (and 134 infants), there were 6/134 (4.5%) events of major congenital anomalies following *in utero* exposure to Simponi vs 599/10,823 (5.5%) events for non-biologic systemic therapy compared to 4.6% in the general population of the study. Confounder-adjusted odds ratios were OR 0.79 (95% CI 0.35-1.81) for Simponi vs. non-biologic systemic therapy and OR 0.95 (95% CI 0.42-2.16) for Simponi vs. the general population, respectively.

Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The available clinical experience is limited. Golimumab should only be used during pregnancy if clearly needed.

Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see sections 4.4 and 4.5).

Breast-feeding
It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Golimumab was shown to pass over to breast milk in monkeys, and because human immunoglobulins are excreted in milk, women must not breast feed during and for at least 6 months after golimumab treatment.

Fertility
No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, showed no relevant effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Simponi has minor influence on the ability to drive and use machines. Dizziness may however occur following administration of Simponi (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
In the controlled period of the pivotal trials in RA, PsA, AS, nr-Axial SpA, and UC, upper respiratory tract infection was the most common adverse reaction (AR) reported in 12.6% of golimumab-treated patients compared with 11.0% of control patients. The most serious ARs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome), haematologic reactions, serious systemic hypersensitivity (including anaphylactic reaction), vasculitis, lymphoma and leukaemia (see section 4.4).

Tabulated list of adverse reactions

ARs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed in Table 1. Within the designated system organ classes, the ARs are listed under headings of frequency and using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1
Tabulated list of ARs

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)
Common:	Bacterial infections (such as cellulitis), lower respiratory tract infection (such as pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess
Uncommon:	Sepsis including septic shock, pyelonephritis
Rare:	Tuberculosis, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), hepatitis B reactivation, bacterial arthritis, infective bursitis
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia, melanoma, Merkel cell carcinoma
Not known:	Hepatosplenic T-cell lymphoma*, Kaposi's sarcoma
Blood and lymphatic system disorders	
Common:	Leukopenia (including neutropenia), anaemia
Uncommon:	Thrombocytopenia, pancytopenia
Rare:	Aplastic anaemia, agranulocytosis
Immune system disorders	
Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis
Endocrine disorders	
Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders	
Uncommon:	Blood glucose increased, lipids increased
Psychiatric disorders	
Common:	Depression, insomnia
Nervous system disorders	
Common:	Dizziness, headache, paraesthesia
Uncommon:	Balance disorders
Rare:	Demyelinating disorders (central and peripheral), dysgeusia
Eye disorders	
Uncommon:	Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritus and irritation)
Cardiac disorders	
Uncommon:	Arrhythmia, ischaemic coronary artery disorders
Rare:	Congestive heart failure (new onset or worsening)

Vascular disorders		
	Common:	Hypertension
	Uncommon:	Thrombosis (such as deep venous and aortic), flushing
	Rare:	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders		
	Common:	Asthma and related symptoms (such as wheezing and bronchial hyperactivity)
	Uncommon:	Interstitial lung disease
Gastrointestinal disorders		
	Common:	Dyspepsia, gastrointestinal and abdominal pain, nausea, gastrointestinal inflammatory disorders (such as gastritis and colitis), stomatitis
	Uncommon:	Constipation, gastro-oesophageal reflux disease
Hepatobiliary disorders		
	Common:	Alanine aminotransferase increased, aspartate aminotransferase increased
	Uncommon:	Cholelithiasis, hepatic disorders
Skin and subcutaneous tissue disorders		
	Common:	Pruritus, rash, alopecia, dermatitis
	Uncommon:	Bullous skin reactions, psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria
	Rare:	Lichenoid reactions, skin exfoliation, vasculitis (cutaneous)
	Not known:	Worsening of symptoms of dermatomyositis
Musculoskeletal and connective tissue disorders		
	Rare:	Lupus-like syndrome
Renal and urinary disorders		
	Rare:	Bladder disorders, renal disorders
Reproductive system and breast disorders		
	Uncommon:	Breast disorders, menstrual disorders
General disorders and administration site conditions		
	Common:	Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia), chest discomfort
	Rare:	Impaired healing
Injury, poisoning and procedural complications		
	Common:	Bone fractures

* Observed with other TNF-blocking agents.

Throughout this section, median duration of follow-up (approximately 4 years) is generally presented for all golimumab use. Where golimumab use is described by dose, the median duration of follow-up varies (approximately 2 years for 50 mg dose, approximately 3 years for 100 mg dose) as patients may have switched between doses.

Description of selected adverse reactions

Infections

In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of golimumab-treated patients (incidence per 100 subject-years: 60.8; 95% CI: 55.0, 67.1) compared with 11.0% of control patients (incidence per 100 subject-years: 54.5; 95% CI: 46.1, 64.0). In controlled and uncontrolled portions of the studies with a median

follow-up of approximately 4 years, the incidence per 100 subject-years of upper respiratory tract infections was 34.9 events; 95% CI: 33.8, 36.0 for golimumab treated patients.

In the controlled period of pivotal trials, infections were observed in 23.0% of golimumab-treated patients (incidence per 100 subject-years: 132.0; 95% CI: 123.3, 141.1) compared with 20.2% of control patients (incidence per 100 subject-years: 122.3; 95% CI: 109.5, 136.2). In controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per 100 subject-years of infections was 81.1 events; 95% CI: 79.5, 82.8 for golimumab treated patients.

In the controlled period of RA, PsA, AS, and nr-Axial SpA trials, serious infections were observed in 1.2% of golimumab-treated patients and 1.2% of control-treated patients. The incidence of serious infections per 100 subject-years of follow-up in the controlled period of RA, PsA, AS, and nr-Axial SpA trials was 7.3; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 2.9; 95% CI: 1.2, 6.0 for the golimumab 50 mg group and 3.6; 95% CI: 1.5, 7.0 for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of golimumab-treated patients compared with 1.5% of control-treated patients. Serious infections observed in golimumab-treated patients included tuberculosis, bacterial infections including sepsis and pneumonia, invasive fungal infections and other opportunistic infections. Some of these infections have been fatal. In the controlled and uncontrolled portions of the pivotal trials with a median follow-up of up to 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 4.1; 95% CI: 3.6, 4.5, in patients receiving golimumab 100 mg and 2.5; 95% CI: 2.0, 3.1, in patients receiving golimumab 50 mg.

Malignancies

Lymphoma

The incidence of lymphoma in golimumab-treated patients during the pivotal trials was higher than expected in the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Lymphoma was diagnosed in 11 subjects (1 in the golimumab 50 mg treatment groups and 10 in the golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.03 (0.00, 0.15) and 0.13 (0.06, 0.24) events for golimumab 50 mg and 100 mg respectively and 0.00 (0.00, 0.57) events for the placebo. The majority of lymphomas occurred in study GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease (see section 4.4).

Malignancies other than lymphoma

In the controlled periods of pivotal trials and through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar to the general population.

In the controlled and uncontrolled periods of pivotal trials with a median follow-up of up to 3 years, non-melanoma skin cancer was diagnosed in 5 placebo-treated, 10 golimumab 50 mg-treated and 31 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.36 (0.26, 0.49) for combined golimumab and 0.87 (0.28, 2.04) for placebo.

In the controlled and uncontrolled period of pivotal trials with a median follow-up of up to 3 years, malignancies besides melanoma, non-melanoma skin cancer and lymphoma were diagnosed in 5 placebo-treated, 21 golimumab 50 mg-treated and 34 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.48 (0.36, 0.62) for combined golimumab and 0.87 (0.28, 2.04) for placebo (see section 4.4).

Cases reported in clinical studies in asthma
In an exploratory clinical study, patients with severe persistent asthma received a golimumab loading dose (150% of the assigned treatment dose) subcutaneously at week 0 followed by golimumab 200 mg, golimumab 100 mg or golimumab 50 mg every 4 weeks subcutaneously through week 52. Eight malignancies in the combined golimumab treatment group (n = 230) and none in the placebo treatment group (n = 79) were reported. Lymphoma was reported in 1 patient, non-melanoma skin cancer in 2 patients, and other malignancies in 5 patients. There was no specific clustering of any type of malignancy.

During the placebo-controlled portion of the study, the incidence (95% CI) of all malignancies per 100 subject-years of follow-up was 3.19 (1.38, 6.28) in the golimumab group. In this study, the incidence (95% CI) per 100 subject-years of follow-up in golimumab-treated subjects was 0.40 (0.01, 2.20) for lymphoma, 0.79 (0.10, 2.86) for non-melanoma skin cancers, and 1.99 (0.64, 4.63) for other malignancies. For placebo subjects, the incidence (95% CI) per 100 subject-years of follow-up of these malignancies was 0.00 (0.00, 2.94). The significance of this finding is unknown.

Neurological events
In the controlled and uncontrolled periods of the pivotal trials with a median follow-up of up to 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg (see section 4.4).

Liver enzyme elevations
In the controlled period of RA and PsA pivotal trials, mild ALT elevations (> 1 and < 3 x upper limit of normal (ULN)) occurred in similar proportions of golimumab and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS and nr-Axial SpA studies, more golimumab-treated patients (26.9%) than control patients (10.6%) had mild ALT elevations. In the controlled and uncontrolled periods of the RA and PsA pivotal trials, with a median follow-up of approximately 5 years, the incidence of mild ALT elevations was similar in golimumab-treated and control patients in RA and PsA studies. In the controlled period of the UC pivotal trials of golimumab induction, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of golimumab-treated and control patients (8.0% to 6.9%, respectively). In controlled and uncontrolled periods of the UC pivotal trials with a median follow-up of approximately 2 years, the proportion of patients with mild ALT elevations was 24.7% in patients receiving golimumab during the maintenance portion of the UC study.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5 x ULN were uncommon and seen in more golimumab-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. In the controlled and uncontrolled periods of RA, PsA and AS pivotal trials, with a median follow-up of 5 years, the incidence of ALT elevations ≥ 5 x ULN was similar in both golimumab-treated and control patients. In general these elevations were asymptomatic and the abnormalities decreased or resolved with either continuation or discontinuation of golimumab or modification of concomitant medicinal products. No cases were reported in the controlled and uncontrolled periods of the nr-Axial SpA study (up to 1 year). In the controlled periods of the pivotal UC trials, of golimumab induction, ALT elevations ≥ 5 x ULN occurred in similar proportions of golimumab-treated patients compared to placebo-treated patients (0.3% to 1.0%, respectively). In the controlled and uncontrolled periods of the pivotal UC trials with a median follow-up of approximately 2 years, the proportion of patients with ALT elevations ≥ 5 x ULN was 0.8% in patients receiving golimumab during the maintenance portion of the UC study.

Within the RA, PsA, AS, and nr-Axial SpA pivotal trials, one patient in an RA trial with pre-existing liver abnormalities and confounding medicinal products treated with golimumab developed non-infectious fatal hepatitis with jaundice. The role of golimumab as a contributing or aggravation factor cannot be excluded.

Injection site reactions
In the controlled periods of pivotal trials, 5.4% of golimumab-treated patients had injection site reactions compared with 2.0% in control patients. The presence of antibodies to golimumab may

increase the risk of injection site reactions. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

In controlled Phase IIb and/or III trials in RA, PsA, AS, nr-Axial SpA, severe persistent asthma, and Phase II/III trials in UC, no patients treated with golimumab developed anaphylactic reactions.

Autoimmune antibodies
In the controlled and uncontrolled periods of pivotal trials through 1 year of follow-up, 3.5% of golimumab-treated patients and 2.3% of control patients were newly ANA-positive (at titres of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients anti-dsDNA negative at baseline was 1.1%.

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

Single doses up to 10 mg/kg intravenously have been administered in a clinical study without dose-limiting toxicity. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors, ATC code: L04AB06

Mechanism of action
Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors.

Pharmacodynamic effects
The binding of human TNF by golimumab was shown to neutralise TNF-α-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. *In vitro*, TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab.

Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with Simponi resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix-metalloproteinase (MMP)-3 and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNF-α were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients. These changes were observed at the first assessment (week 4) after the initial Simponi administration and were generally maintained through week 24.

Clinical efficacy

Rheumatoid arthritis
The efficacy of Simponi was demonstrated in three multi-centre, randomised, double-blind, placebo-controlled studies in over 1500 patients ≥ 18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening. Patients had at least 4 swollen and 4 tender joints. Simponi or placebo were subcutaneously administered every 4 weeks.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. Patients receiving placebo + MTX were switched to Simponi 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

GO-AFTER evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomised to receive placebo, Simponi 50 mg, or Simponi 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Simponi 50 mg + MTX.

In GO-FORWARD, the (co-) primary endpoints were the percentage of patients achieving an ACR 20 response at week 14 and the improvement from baseline in Health Assessment Questionnaire (HAQ) at week 24. In GO-AFTER, the primary endpoint was the percentage of patients achieving an ACR 20 response at week 14. In GO-BEFORE, the co-primary endpoints were the percentage of patients achieving ACR 50 response at week 24 and the change from baseline in the van der Heijde-modified Sharp (vdH-S) score at week 52. In addition to the primary endpoint(s), additional assessments of the impact of Simponi treatment on the signs and symptoms of arthritis, radiographic response, physical function and health-related quality of life were performed.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens with concomitant MTX, through week 104 in GO-FORWARD and GO-BEFORE and through week 24 in GO-AFTER. In each of the RA studies by study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms
Key ACR results for the Simponi 50 mg dose at weeks 14, 24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 2 and are described below. Responses were observed at the first assessment (week 4) after the initial Simponi administration.

In GO-FORWARD, among 89 subjects randomised to Simponi 50 mg + MTX, 48 were still on this treatment at week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving Simponi than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 2
Key efficacy outcomes from the controlled portions of GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	Simponi 50 mg + MTX	Placebo	Simponi 50 mg	Placebo + MTX	Simponi 50 mg + MTX
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA
Week 24	28%	60%*	16%	31% p = 0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p = 0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p = 0.008	2%	10% p = 0.005	NA	NA
Week 24	5%	20%*	2%	9% p = 0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.
* $p \leq 0.001$
NA: Not Applicable

In GO-BEFORE the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Simponi 50 and 100 mg + MTX groups vs MTX alone for ACR50) was not statistically significant at week 24 (p = 0.053). At week 52 in the overall population, the percentage of patients in the Simponi 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 2). Additional analyses were performed in subsets representative of the indicated population of patients with severe, active and progressive RA. A generally greater effect of Simponi 50 mg + MTX versus MTX alone was demonstrated in the indicated population compared with the overall population.

In GO-FORWARD and GO-AFTER, clinically meaningful and statistically significant responses in Disease Activity Scale (DAS)28 were observed at each prespecified time point, at week 14 and at week 24 ($p \leq 0.001$). Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 responses were similar from week 104 through week 256.

In GO-BEFORE, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At week 52, 15% of patients in the Simponi 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group (p = 0.018). Among 159 subjects randomised to Simponi 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response were observed from week 104 through week 256.

Radiographic response
In GO-BEFORE the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space

narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Simponi 50 mg dose at week 52 are presented in Table 3.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the Simponi treatment group than in the control group (p = 0.003). The radiographic effects observed at week 52 were maintained through week 104. Among patients remaining in the study and treated with Simponi, radiographic effects were similar from week 104 through week 256.

Table 3
Radiographic mean (SD) changes from baseline in total vdH-S score at week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Simponi 50 mg + MTX**
n[a]	**160**	**159**
Total Score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion Score		
Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.7 (2.8)	0.5 (2.1)
JSN Score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)**

[a] n reflects randomised patients
* p = 0.015
** p = 0.044

Physical function and health-related quality of life
Physical function and disability were assessed as a separate endpoint in GO-FORWARD and GO-AFTER using the disability index of the HAQ DI. In these studies, Simponi demonstrated clinically meaningful and statistically significant improvement in HAQ DI from baseline versus control at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement in HAQ DI was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement in HAQ DI was similar from week 104 through week 256.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with Simponi versus placebo at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement of the SF-36 physical component was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement of the SF-36 physical component was similar from week 104 through week 256. In GO-FORWARD and GO-AFTER, statistically significant improvements were observed in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F).

Psoriatic arthritis
The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months and had at least mild psoriatic disease. Patients with each sub-type of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). Previous treatment with an anti-TNF agent was not allowed. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg, or

Simponi 100 mg. Patients receiving placebo were switched to Simponi 50 mg after week 24. Patients entered an open label long-term extension at week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at week 14 and change from baseline in total PsA modified vdH-S score at week 24.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 104. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms
Key results for the 50 mg dose at weeks 14 and 24 are shown in Table 4 and described below.

Table 4
Key efficacy outcomes from GO-REVEAL

	Placebo	Simponi 50 mg*
n[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	**9%**	**51%**
Week 24	12%	52%
ACR 50		
Week 14	2%	30%
Week 24	4%	32%
ACR 70		
Week 14	1%	12%
Week 24	1%	19%
PASI[b] 75[c]		
Week 14	3%	40%
Week 24	1%	56%

* $p < 0.05$ for all comparisons;

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

[b] *Psoriasis Area and Severity Index*

[c] Based on the subset of patients with ≥ 3% BSA involvement at baseline, 79 patients (69.9%) in the placebo group and 109 (74.3%) in the Simponi 50 mg group.

Responses were observed at the first assessment (week 4) after the initial Simponi administration. Similar ACR 20 responses at week 14 were observed in patients with polyarticular arthritis with no rheumatoid nodules and asymmetric peripheral arthritis PsA subtypes. The number of patients with other PsA subtypes was too small to allow meaningful assessment. Responses observed in the Simponi treated groups were similar in patients receiving and not receiving concomitant MTX. Among 146 patients randomised to Simponi 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 ($p < 0.05$).

At week 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Simponi-treated patients. Simponi treatment resulted in significant improvement in physical function as assessed by HAQ DI, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36. Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 and HAQ DI

responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 and HAQ DI responses were similar from week 104 through week 256.

Radiographic response
Structural damage in both hands and feet was assessed radiographically by the change from baseline in the vdH-S score, modified for PsA by addition of hand distal interphalangeal (DIP) joints.

Simponi 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean ± SD score was 0.27 ± 1.3 in the placebo group compared with -0.16 ± 1.3 in the Simponi group; p = 0.011). Out of 146 patients who were randomised to Simponi 50 mg, 52 week X-ray data were available for 126 patients, of whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline. Among patients remaining in the study and treated with Simponi, similar rates of patients showed no progression from baseline from week 104 through week 256.

Axial spondyloarthritis
Ankylosing spondylitis
The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and a VAS for total back pain of ≥ 4, on a scale of 0 to 10 cm). Patients enrolled in this study had active disease despite current or previous NSAID or DMARD therapy and had not previously been treated with anti-TNF therapy. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg and Simponi 100 mg and were allowed to continue concomitant DMARD therapy (MTX, SSZ and/or HCQ). The primary endpoint was the percentage of patients achieving Ankylosing Spondylitis Assessment Study Group (ASAS) 20 response at week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

Key results for the 50 mg dose are shown in Table 5 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 24. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Table 5
Key efficacy outcomes from GO-RAISE

	Placebo	Simponi 50 mg*
n[a]	78	138
Responders, % of patients		
ASAS 20		
Week 14	**22%**	**59%**
Week 24	23%	56%
ASAS 40		
Week 14	15%	45%
Week 24	15%	44%
ASAS 5/6		
Week 14	8%	50%
Week 24	13%	49%

* $p \leq 0.001$ for all comparisons
[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

Among patients remaining in the study and treated with Simponi, the proportion of patients with an ASAS 20 and ASAS 40 response were similar from week 24 through week 256.

Statistically significant responses in BASDAI 50, 70 and 90 ($p \leq 0.017$) were also seen at weeks 14 and 24. Improvements in key measures of disease activity were observed at the first assessment

(week 4) after the initial Simponi administration and were maintained through week 24. Among patients remaining in the study and treated with Simponi, similar rates of change from baseline in BASDAI were observed from week 24 through week 256. Consistent efficacy was seen in patients regardless of use of DMARDs (MTX, sulfasalazine and/or hydroxychloroquine), HLA-B27 antigen status or baseline CRP levels as assessed by ASAS 20 responses at week 14.

Simponi treatment resulted in significant improvements in physical function as assessed by changes from baseline in BASFI at weeks 14 and 24. Health-related quality of life as measured by the physical component score of the SF-36 was also improved significantly at weeks 14 and 24. Among patients remaining in the study and treated with Simponi, improvements in physical function and health-related quality of life were similar from week 24 through week 256.

Non-radiographic axial spondyloarthritis

GO-AHEAD

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-AHEAD) in 197 adult patients with severe active nr-Axial SpA (defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS). Patients enrolled in this study had active disease (defined as a BASDAI ≥ 4 and a Visual Analogue Scale (VAS) for total back pain of ≥ 4, each on a scale of 0-10 cm) despite current or previous NSAID therapy and had not previously been treated with any biological agents including anti-TNF therapy. Patients were randomly assigned to placebo or Simponi 50 mg administered subcutaneously every 4 weeks. At week 16, patients entered an open label period in which all patients received Simponi 50 mg administered subcutaneously every 4 weeks through week 48 with efficacy assessments performed through week 52 and safety follow-up through week 60. Approximately 93% of patients who were receiving Simponi at the beginning of the open-label extension (week 16) remained on treatment through the end of the study (week 52). Analyses were performed on both the All Treated (AT, N = 197) and Objective Signs of Inflammation (OSI, N = 158, defined by elevated CRP and/or evidence of sacroiliitis on MRI at baseline) populations. Placebo-controlled efficacy data were collected and analysed through week 16. The primary endpoint was the proportion of patients achieving ASAS 20 response at week 16. Key results are shown in Table 6 and described below.

Table 6
Key efficacy outcomes from GO-AHEAD at week 16

Improvements in signs and symptoms				
	All treated population (AT)		Objective signs of inflammation population (OSI)	
	Placebo	Simponi 50 mg	Placebo	Simponi 50 mg
n[a]	100	97	80	78
Responders, % of patients				
ASAS 20	40%	71%**	38%	77%**
ASAS 40	23%	57%**	23%	60%**
ASAS 5/6	23%	54%**	23%	63%**
ASAS Partial Remission	18%	33%*	19%	35%*
ASDAS-C [b] < 1.3	13%	33%*	16%	35%*
BASDAI 50	30%	58%**	29%	59%**
Inhibition of inflammation in sacroiliac (SI) joints as measured by MRI				
	Placebo	Simponi 50 mg	Placebo	Simponi 50 mg
n[c]	87	74	69	61
Mean change in SPARCC[d] MRI sacroiliac joint score	-0.9	-5.3**	-1.2	-6.4**

[a] n reflects randomised and treated patients
[b] Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (AT-Placebo, N = 90; AT-Simponi 50 mg, N = 88; OSI-Placebo, N = 71; OSI-Simponi 50 mg, N = 71)
[c] n reflects number of patients with baseline and week 16 MRI data
[d] SPARCC (Spondyloarthritis Research Consortium of Canada)
** $p < 0.0001$ for Simponi *vs* placebo comparisons
* $p < 0.05$ for Simponi *vs* placebo comparisons

Statistically significant improvements in signs and symptoms of severe active nr-Axial SpA were demonstrated in patients treated with Simponi 50 mg compared to placebo at week 16 (Table 6). Improvements were observed at the first assessment (week 4) after the initial Simponi administration. SPARCC score as measured by MRI showed statistically significant reductions in SI joint inflammation at week 16 in patients treated with Simponi 50 mg compared to placebo (Table 6). Pain as assessed by the Total Back Pain and Nocturnal Back Pain VAS, and disease activity as measured by ASDAS-C also showed statistically significant improvement from baseline to week 16 in patients treated with Simponi 50 mg compared to placebo ($p < 0.0001$).

Statistically significant improvements in spinal mobility as assessed by BASMI (Bath Ankylosing Spondylitis Metrology Index) and in physical function as assessed by the BASFI were demonstrated in Simponi 50 mg-treated patients as compared to placebo-treated patients ($p < 0.0001$). Patients treated with Simponi experienced significantly more improvements in health-related quality of life as assessed by ASQoL, EQ-5D, and physical and mental components of SF-36, and experienced significantly more improvements in productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI questionnaire than patients receiving placebo.

For all of the endpoints described above, statistically significant results were also demonstrated in the OSI population at week 16.

In both the AT and OSI populations, the improvements in signs and symptoms, spinal mobility, physical function, quality of life, and productivity observed at week 16 among patients treated with Simponi 50 mg continued in those remaining in the study at week 52.

GO-BACK

The efficacy and safety of continued golimumab treatment (full or reduced dosing frequency) compared with treatment withdrawal was assessed in adult patients (18-45 years of age) with active nr-axSpA who demonstrated sustained remission during 10 months of monthly treatment with open-label Simponi (GO-BACK). Eligible patients (who achieved a clinical response by Month 4 and an inactive disease status (ASDAS < 1.3) at both Months 7 and 10) entering the double-blind withdrawal phase were randomised to continued monthly treatment with Simponi (full-treatment regimen, N = 63), every 2-month treatment with Simponi (reduced treatment regimen, N = 63) or monthly placebo treatment (treatment withdrawal, N = 62) for up to approximately 12 months.

The primary efficacy endpoint was the proportion of patients without a flare of disease activity. Patients who experienced a flare, i.e., had an ASDAS collected at 2 consecutive assessments that both showed either an absolute score of ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (end of open-label period), reinitiated monthly Simponi in an open-label retreatment phase to characterise clinical response.

Clinical response after double-blind treatment withdrawal
Among the 188 patients with inactive disease who received at least one dose of double-blind treatment, a significantly ($p < 0.001$) greater proportion of patients did not experience a disease flare when continuing Simponi with either the full-treatment (84.1%), or reduced treatment (68.3%) regimens compared with treatment withdrawal (33.9%) (Table 7).

Table 7
Analysis of the proportion of participants without a flare[a]
Full analysis set population (Period 2 – Double-blind)

Treatment	n/N	%	Difference in % vs Placebo	
			Estimate (95% CI)[b]	p-Value[b]
GLM SC QMT	53/63	84.1	50.2 (34.1, 63.6)	< 0.001
GLM SC Q2MT	43/63	68.3	34.4 (17.0, 49.7)	< 0.001
Placebo	21/62	33.9		

Full Analysis Set includes all randomised participants who attained inactive disease in period 1 and received at least one dose of blinded study treatment.

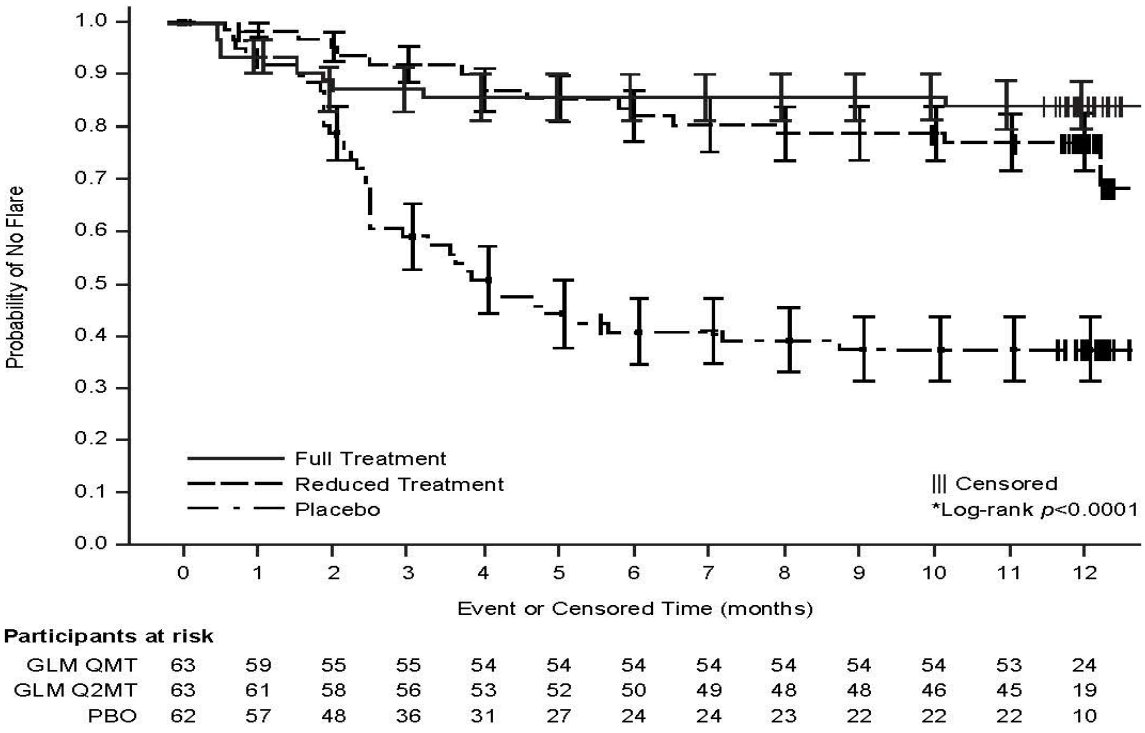
[a] Defined as ASDAS at 2 consecutive visits that both show either absolute score ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23).

[b] Type I error rate over the multiple treatment comparisons (GLM SC QMT vs Placebo and GLM SC Q2MT vs Placebo) was controlled using a sequential (step-down) testing procedure. Derived based on the stratified Miettinen and Nurminen method with CRP level (> 6 mg/L or ≤ 6 mg/L) as stratification factor.

Participants who discontinued period 2 prematurely and prior to a 'flare' will be counted as having a 'flare'.
N = Total number of participants; n = number of participants without a flare; GLM = golimumab; SC = subcutaneous, QMT = monthly dosing; Q2MT = every other month dosing.

The difference in time-to-first flare between the treatment withdrawal group and either of the Simponi Treatment groups is shown in Figure 1 (log-rank p < 0.0001 for each comparison). In the placebo group, flares started approximately 2 months after Simponi was withdrawn, with the majority of flares occurring within 4 months of treatment withdrawal (Figure 1).

Figure 1: Kaplan-Meier Analysis of Time-to-First Flare



*Endpoint not adjusted for multiplicity. Stratified by CRP level (> 6 mg/L or ≤ 6 mg/L). Flare was defined as an ASDAS at 2 consecutive visits that both showed either an absolute score of ≥ 2.1 or a post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23). Participants who did not flare were censored at the time of discontinuation or Month 13 of Period 2 double-blind treatment. Start of Period 2 represents Day 1 of the Kaplan-Meier analysis for the full analysis set.

Clinical response to retreatment for a disease flare
Clinical response was defined as a BASDAI improvement of ≥ 2 or ≥ 50% relative to the mean of the 2 consecutive BASDAI scores ascribed to the disease flare. Of the 53 participants in the reduced dosing or treatment withdrawal regimens who had a confirmed disease flare, 51 (96.2%) attained a

clinical response to Simponi within the first 3 months of retreatment, although fewer patients (71.7%) were able to sustain it for all 3 months.

Ulcerative colitis
The efficacy of Simponi was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients.

The induction study (PURSUIT-Induction) evaluated patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) who had an inadequate response to or failed to tolerate conventional therapies, or were corticosteroid dependent. In the dose confirming portion of the study, 761 patients were randomised to receive either 400 mg Simponi SC at week 0 and 200 mg at week 2, 200 mg Simponi SC at week 0 and 100 mg at week 2, or placebo SC at weeks 0 and 2. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. The efficacy of Simponi through week 6 was assessed in this study.

The results of the maintenance study (PURSUIT-Maintenance) were based on evaluation of 456 patients who achieved clinical response from previous induction with Simponi. Patients were randomised to receive Simponi 50 mg, Simponi 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, and/or immunomodulatory agents were permitted. Corticosteroids were to be tapered at the start of the maintenance study. The efficacy of Simponi through week 54 was assessed in this study. Patients who completed the maintenance study through week 54 continued treatment in a study extension, with efficacy evaluated through week 216. Efficacy evaluation in the study extension was based on changes in corticosteroid use, Physician's Global Assessment (PGA) of disease activity, and improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire (IBDQ).

Table 8
Key efficacy outcomes from PURSUIT - Induction and PURSUIT - Maintenance

PURSUIT-Induction			
	Placebo N = 251	**Simponi** **200/100 mg** N = 253	
Percentage of patients			
Patients in clinical response at week 6[a]	30%	51%**	
Patients in clinical remission at week 6[b]	6%	18%**	
Patients with mucosal healing at week 6[c]	29%	42%*	
PURSUIT-Maintenance			
	Placebo[d] N = 154	**Simponi** **50 mg** N = 151	**Simponi** **100 mg** N = 151
Percentage of patients			
Maintenance of response (Patients in clinical response through week 54)[e]	31%	47%*	50%**
Sustained remission (Patients in clinical remission at both week 30 and week 54)[f]	16%	23%[g]	28%*

N = number of patients
** $p \leq 0.001$
* $p \leq 0.01$
[a] defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.
[b] Defined as a Mayo score ≤ 2 points, with no individual subscore > 1
[c] Defined as 0 or 1 on the endoscopy subscore of the Mayo score.
[d] Simponi induction only.
[e] Patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). Therefore, a patient who maintained response was in a state of continuous clinical response at each evaluation through week 54.
[f] A patient had to be in remission at both weeks 30 and 54 (without demonstrating a loss of response at any time point through week 54) to achieve durable remission.
[g] In patients weighing less than 80 kg, a greater proportion of patients who received 50 mg maintenance therapy showed sustained clinical remission compared with those who received placebo.

More Simponi-treated patients demonstrated sustained mucosal healing (patients with mucosal healing at both week 30 and week 54) in the 50 mg group (42%, nominal $p < 0.05$) and 100 mg group (42%, $p < 0.005$) compared with patients in the placebo group (27%).

Among the 54% of patients (247/456) who were receiving concomitant corticosteroids at the start of PURSUIT-Maintenance, the proportion of patients who maintained clinical response through week 54 and were not receiving concomitant corticosteroids at week 54 was greater in the 50 mg group (38%, 30/78) and 100 mg group (30%, 25/82) compared with the placebo group (21%, 18/87). The proportion of patients who eliminated corticosteroids by week 54 was greater in the 50 mg group (41%, 32/78) and 100 mg group (33%, 27/82) compared with the placebo group (22%, 19/87). Among patients who entered the study extension, the proportion of subjects who remained corticosteroid free was generally maintained through week 216.

Patients who did not achieve clinical response at week 6 in the PURSUIT-Induction studies were dosed Simponi 100 mg every 4 weeks in the PURSUIT-Maintenance study. At week 14, 28% of these patients achieved response defined by partial Mayo score (decreased by ≥ 3 points compared with start of induction). At week 54, the clinical outcomes observed in these patients were similar to the clinical outcomes reported for the patients achieving clinical response at week 6.

At week 6, Simponi significantly improved quality of life as measured by change from baseline in a disease specific measure, IBDQ (inflammatory bowel disease questionnaire). Among patients who received Simponi maintenance treatment, the improvement in quality of life as measured by IBDQ was maintained through week 54.

Approximately 63% of patients who were receiving Simponi at the beginning of the study extension (week 56), remained on treatment through the end of the study (last golimumab administration at week 212).

Immunogenicity
Across the Phase III RA, PsA and AS studies through week 52, antibodies to golimumab were detected in 5% (105/2062) of golimumab treated patients and, where tested, nearly all antibodies were neutralising *in vitro*. Similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without MTX (approximately 3% [41/1235] versus 8% [64/827], respectively).

In nr-Axial SpA, antibodies to golimumab were detected in 7% (14/193) of golimumab treated patients through week 52.

In the Phase II and III UC studies through week 54, antibodies to golimumab were detected in 3% (26/946) of golimumab treated patients. Sixty-eight percent (21/31) of antibody-positive patients had neutralising antibodies *in vitro*. Treatment with concomitant immunomodulators (azathioprine, 6-mercaptopurine and MTX) resulted in a lower proportion of patients with antibodies to golimumab

than patients receiving golimumab without immunomodulators (1% (4/308) versus 3% (22/638), respectively). Of patients that continued in the study extension and had evaluable samples through week 228, antibodies to golimumab were detected in 4% (23/604) of golimumab treated patients. Eighty-two percent (18/22) of antibody-positive patients had neutralising antibodies *in vitro*.

The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.8). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

Because immunogenicity analyses are product- and assay-specific, comparison of antibody rates with those from other products is not appropriate.

5.2 Pharmacokinetic properties

Absorption
Following a single subcutaneous administration of golimumab to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A subcutaneous injection of 50 mg golimumab to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/mL.

Following a single subcutaneous injection of 100 mg, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since golimumab exhibited approximately dose proportional PK following a subcutaneous administration, the absolute bioavailability of a golimumab 50 mg or 200 mg dose is expected to be similar.

Distribution
Following a single IV administration, the mean volume of distribution was 115 ± 19 mL/kg.

Elimination
The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg. Terminal half-life value was estimated to be approximately 12 ± 3 days in healthy subjects and similar values were observed in patients with RA, PsA, AS, or UC.

When 50 mg golimumab was administered subcutaneously to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by week 12. With concomitant use of MTX, treatment with 50 mg golimumab subcutaneously every 4 weeks resulted in a mean (± standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 μg/mL in patients with active PsA and approximately 0.8 ± 0.4 μg/mL in patients with AS. Steady-state trough mean serum golimumab concentrations in patients with nr-Axial SpA were similar to those observed in patients with AS following subcutaneous administration of 50 mg golimumab every 4 weeks.

Patients with RA, PsA or AS who did not receive concomitant MTX had approximately 30% lower steady-state trough concentrations of golimumab than those who received golimumab with MTX. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. However, population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

Following induction doses of 200 mg and 100 mg golimumab at week 0 and 2, respectively, and maintenance doses of 50 mg or 100 mg golimumab subcutaneously every 4 weeks thereafter to patients with UC, serum golimumab concentrations reached steady state approximately 14 weeks after the start of therapy. Treatment with 50 mg or 100 mg golimumab subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 0.9 ± 0.5 μg/mL and 1.8 ± 1.1 μg/mL, respectively.

In UC patients treated with 50 mg or 100 mg golimumab subcutaneously every 4 weeks, concomitant use of immunomodulators did not have a substantial effect on steady-state trough levels of golimumab.

Patients who developed antibodies to golimumab generally had low trough steady-state serum concentrations of golimumab (see section 5.1).

Linearity
Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose. Following a single SC dose in healthy subjects, approximately dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg.

Effect of weight on pharmacokinetics
There was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

No mutagenicity studies, animal fertility studies nor long-term carcinogenic studies have been conducted with golimumab.

In a fertility and general reproductive function study in mouse, using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, the number of pregnant mice was reduced. It is not known whether this finding was due to effects on the males and/or the females. In a developmental toxicity study conducted in mice following administration of the same analogous antibody, and in cynomolgus monkeys using golimumab, there was no indication of maternal toxicity, embryotoxicity or teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years

6.4 Special precautions for storage

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

Keep the pre-filled pen in the outer carton in order to protect it from light.
Simponi may be stored at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 30 days from the date removed from the refrigerator).

Once Simponi has been stored at room temperature, it should not be returned to refrigerated storage. Simponi must be discarded if not used within the 30 days of room temperature storage.

6.5 Nature and contents of container

Simponi 100 mg solution for injection in pre-filled pen
1 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex) in a pre-filled pen. Simponi is available in packs containing 1 pre-filled pen and multipacks containing 3 (3 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Simponi is supplied in a single use pre-filled pen called SmartJect. Each pack is provided with instructions for use that fully describe the use of the pen. After removing the pre-filled pen from the refrigerator it should be allowed to reach room temperature by waiting for 30 minutes, before injecting Simponi. The pen should not be shaken.

The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for solutions containing protein. Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

Comprehensive instructions for the preparation and administration of Simponi in a pre-filled pen are given in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/005 1 pre-filled pen
EU/1/09/546/006 3 pre-filled pens

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 October 2009
Date of latest renewal: 19 June 2014

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

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy
Co. Cork
Ireland

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

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**

The educational programme consists of a Patient Card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professional(s) treating the patient about on-going treatment with the product.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN FOR PAEDIATRIC USE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Simponi 45 mg/0.45 mL solution for injection in pre-filled pen
golimumab
For paediatric patients < 40 kg

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.45 mL pre-filled pen contains 45 mg golimumab
1 mL contains 100 mg golimumab.

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (VarioJect)
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 45 mg/0.45 mL

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

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN FOR PAEDIATRIC USE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Simponi 45 mg/0.45 mL injection
golimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.45 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Simponi 50 mg solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.5 mL pre-filled pen contains 50 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (SmartJect)
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 50 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

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 PRE-FILLED PEN AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 50 mg solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.5 mL pre-filled pen contains 50 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (SmartJect)
1 pre-filled pen
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR MULTIPACK COMPRISING 3 PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 50 mg
solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.5 mL pre-filled pen contains 50 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (SmartJect)
Multipack: 3 (3 packs of 1) pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen 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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/002 (3 packs, each containing 1 pre-filled pen)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 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

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Simponi 50 mg solution for injection
golimumab
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

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Simponi 50 mg solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.5 mL pre-filled syringe contains 50 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 50 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

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 PRE-FILLED SYRINGE AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 50 mg solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.5 mL pre-filled syringe contains 50 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR MULTIPACK COMPRISING 3 PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 50 mg
solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.5 mL pre-filled syringe contains 50 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
Multipack: 3 (3 packs of 1) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe 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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/004 (3 packs, each containing 1 pre-filled syringe)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 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

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Simponi 50 mg
injection
golimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 mL pre-filled pen contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (SmartJect)
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 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

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 PRE-FILLED PEN AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 mL pre-filled pen contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (Smartject)
1 pre-filled pen
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR MULTIPACK COMPRISING 3 PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg
solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 mL pre-filled pen contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (SmartJect)
Multipack: 3 (3 packs of 1) pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen 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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/006 (3 packs, each containing 1 pre-filled pen)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 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

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Simponi 100 mg solution for injection
golimumab
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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 mL pre-filled syringe contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 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

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 PRE-FILLED SYRINGE AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 mL pre-filled syringe contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP
EXP, if stored at room temperature_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light
Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiry date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR MULTIPACK COMPRISING 3 PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg
solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 mL pre-filled syringe contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433), water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
Multipack: 3 (3 packs of 1) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
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

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe 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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/008 (3 packs, each containing 1 pre-filled syringe)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 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

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Simponi 100 mg
injection
golimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

Simponi Patient Card

This Patient Card contains important safety information that you need to be aware of before and during treatment with Simponi.

Show this card to any doctor involved in your treatment.

1. Infections

When you are treated with Simponi, you might get infections more easily. Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

1.1 Prior to Simponi treatment:

- Tell your doctor if you have an infection. You must not be treated with Simponi if you have tuberculosis (TB) or any other severe infection.
- You should be screened for TB. It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had TB. Ask your doctor to record the type and date of the last screening(s) for TB below:

  Test _____ Test _____
  Date _____ Date _____
  Result _____ Result _____
- Tell your doctor if you know or suspect you are a carrier of the hepatitis B virus.

1.2 During and after Simponi treatment:

- Seek medical attention immediately if you develop symptoms of an infection, such as fever, tiredness, (persistent) cough, shortness of breath, or flu-like signs, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.

2. Pregnancy and vaccinations

In case you have received Simponi while you were pregnant, it is important that you inform your baby's doctor about it before your baby receives any vaccine. Your baby should not receive a 'live vaccine', such as BCG (used to prevent tuberculosis) within 6 months after your last Simponi injection during pregnancy.

3. Dates of Simponi treatment

1st administration: _____

Subsequent administrations: _____
_____

It is important that you and your doctor record the brand name and batch number of your medicine.

4. Other information

Patient's Name: _____
Doctor's Name: _____
Doctor's Phone: _____

- Please make sure you also have a list of all other medicines that you are using with you at any visit to a health care professional.

- Keep this card with you for 6 months after the last Simponi dose, since side effects may occur a long time after your last dose of Simponi.

- Read the Simponi package leaflet carefully before you start using this medicine.

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Simponi 45 mg/0.45 mL solution for injection in pre-filled pen
For paediatric patients below 40 kg
golimumab

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.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

Your doctor will also give you a Patient Card, which contains important safety information you need to be aware of before and during your treatment with Simponi.

What is in this leaflet

1. What Simponi is and what it is used for
2. What you need to know before you use Simponi
3. How to use Simponi
4. Possible side effects
5. How to store Simponi
6. Contents of the pack and other information

1. What Simponi is and what it is used for

Simponi contains the active substance called golimumab.

Simponi belongs to a group of medicines called 'TNF blockers'. It is used **in children** 2 years of age and older for the treatment of polyarticular juvenile idiopathic arthritis and **in children** 2 years of age and older and above 15 kg for the treatment of paediatric ulcerative colitis.

Simponi works by blocking the action of a protein called 'tumour necrosis factor alpha' (TNF-α). This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body.

Polyarticular juvenile idiopathic arthritis
Polyarticular juvenile idiopathic arthritis is an inflammatory disease that causes joint pain and swelling in children. If you have polyarticular juvenile idiopathic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simponi in combination with methotrexate to treat the disease.

Paediatric ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simponi to treat your disease.

2. What you need to know before you use Simponi

Do not use Simponi
- If you are allergic (hypersensitive) to golimumab or any of the other ingredients of this medicine (listed in Section 6).
- If you have tuberculosis (TB) or any other severe infection.

- If you have moderate or severe heart failure.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Simponi.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Simponi.

Infections
Tell your doctor straight away if you already have or get any symptoms of infection, during or after your treatment with Simponi. Symptoms of infection include fever, cough, shortness of breath, flu-like symptoms, diarrhoea, wounds, dental problems or a burning feeling when urinating.
- You may get infections more easily while using Simponi.
- Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

Tuberculosis (TB)
Tell your doctor straight away if symptoms of TB appear during or after your treatment. Symptoms of TB include persistent cough, weight loss, tiredness, fever or night sweats.
- Cases of TB have been reported in patients treated with Simponi, in rare occasions even in patients who have been treated with medicines for TB. Your doctor will test you to see if you have TB. Your doctor will record these tests on your Patient Card.
- It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had or has TB.
- If your doctor feels that you are at risk of TB, you may be treated with medicines for TB before you begin using Simponi.

Hepatitis B virus (HBV)
- Tell your doctor if you are a carrier or if you have or have had HBV before you are given Simponi.
- Tell your doctor if you think you might be at risk of contracting HBV
- Your doctor should test you for HBV
- Treatment with TNF blockers such as Simponi may result in reactivation of HBV in patients who carry this virus, which can be life-threatening in some cases.

Invasive fungal infections
If you have lived in or travelled to an area where infections caused by specific type of fungi that can affect the lungs or other parts of the body (called histoplasmosis, coccidioidomycosis, or blastomycosis), are common, tell your doctor straight away. Ask your doctor if you don't know if these fungal infections are common in the area in which you have lived or travelled.

Cancer and lymphoma
Tell your doctor if you have ever been diagnosed with lymphoma (a type of blood cancer) or any other cancer before you use Simponi.
- If you use Simponi or other TNF blockers, your risk for developing lymphoma or another cancer may increase.
- Patients with severe rheumatoid arthritis and other inflammatory diseases, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
- There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death.
- On rare occasions, a specific and severe type of lymphoma called hepatosplenic T-cell lymphoma has been observed in patients taking other TNF-blockers. Most of these patients were adolescent or young adult males. This type of cancer has usually resulted in death. Almost all of these patients had also received medicines known as azathioprine or 6-mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Simponi.

- Patients with severe persistent asthma, chronic obstructive pulmonary disease (COPD), or are heavy smokers may be at increased risk for cancer with Simponi treatment. If you have severe persistent asthma, COPD or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.
- Some patients treated with golimumab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Heart failure
Tell your doctor straight away if you get new or worsening symptoms of heart failure. Symptoms of heart failure include shortness of breath or swelling of your feet.
- New and worsening congestive heart failure has been reported with TNF blockers, including Simponi. Some of these patients died.
- If you have mild heart failure and you are being treated with Simponi, you must be closely monitored by your doctor.

Nervous system disease
Tell your doctor straight away if you have ever been diagnosed with or develop symptoms of a demyelinating disease such as multiple sclerosis. Symptoms may include changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body. Your doctor will decide if you should receive Simponi.

Operations or dental procedures
- Talk to your doctor if you are going to have any operations or dental procedures.
- Tell your surgeon or dentist performing the procedure that you are having treatment with Simponi by showing them your Patient Card.

Autoimmune disease
Tell your doctor if you develop symptoms of a disease called lupus. Symptoms include persistent rash, fever, joint pain and tiredness.
- On rare occasions, people treated with TNF blockers have developed lupus.

Blood disease
In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Vaccinations
Talk to your doctor if you have had, or are due to have a vaccine.
- You should not receive certain (live) vaccines while using Simponi.
- Certain vaccinations may cause infections. If you received Simponi while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Simponi use so they can decide when your baby should receive any vaccine.

Talk to your child’s doctor regarding vaccinations for your child. If possible, your child should be up to date with all vaccinations before using Simponi.

Therapeutic infectious agents
Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Allergic reactions
Tell your doctor straight away if you develop symptoms of an allergic reaction after your treatment with Simponi. Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles.

- Some of these reactions may be serious or, rarely, life-threatening.
- Some of these reactions occurred after the first administration of Simponi.

Children
Simponi is not recommended for children less than 2 years of age with polyarticular juvenile idiopathic arthritis or paediatric ulcerative colitis because it has not been studied in these groups.

Other medicines and Simponi

- Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including any other medicines to treat polyarticular juvenile idiopathic arthritis.
- You should not take Simponi with medicines containing the active substance anakinra or abatacept. These medicines are used for the treatment of rheumatic diseases.
- Tell your doctor or pharmacist if you are taking any other medicines that affect your immune system.
- You should not receive certain (live) vaccines while using Simponi.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Pregnancy and breast-feeding
Talk to your doctor before using Simponi if:

- You are pregnant or are planning to become pregnant while using Simponi. There is limited information about the effects of this medicine in pregnant women. If you are being treated with Simponi, you must avoid becoming pregnant by using adequate contraception during your treatment and for at least 6 months after the last Simponi injection. Simponi should only be used during pregnancy if it is clearly necessary for you.
- Before starting breast-feeding, your last treatment with Simponi must be at least 6 months ago. You must stop breast-feeding if you are to be given Simponi.
- If you received Simponi during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Simponi use before the baby receives any vaccine (for more information see section on vaccination).

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Simponi has minor influence on your ability to ride bicycles, drive and use tools or machines. Dizziness may however occur after you take Simponi. If this happens, do not ride bicycles, drive or use any tools or machines.

Simponi contains latex, sorbitol and polysorbate
Latex sensitivity
A part of the pre-filled pen, the needle cover, contains latex. Because latex may cause severe allergic reactions, talk to your doctor before using Simponi if you or your carer are allergic to latex.

Sorbitol intolerance
This medicine contains 18.5 mg sorbitol (E420) in each pre-filled pen. Each 0.05 mL medicine contains 2.05 mg sorbitol (E420).

Polysorbate 80
This medicine contains 0.068 mg of polysorbate 80 (E433) in each pre-filled pen. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Simponi

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

How much Simponi is given
Polyarticular juvenile idiopathic arthritis in children 2 years of age and older:

- Children weighing *less than 40 kg*:
  The recommended dose of Simponi for children weighing less than 40 kg depends on their weight and height. Your doctor will tell you the correct dose to use. The dose should be given once a month, on the same date each month.

- Children weighing *at least 40 kg*:
  For children with body weight of at least 40 kg, a fixed dose 50 mg pre-filled pen or pre-filled syringe is available. For the 50 mg dose, see section 3 “How to use Simponi” of the Simponi 50 mg pre-filled pen or pre-filled syringe package leaflet.

- Talk to your doctor before you take the fourth dose. Your doctor will determine if you should continue Simponi treatment.

Paediatric ulcerative colitis in children 2 years of age and older weighing at least 15 kg:

- Children weighing at least 15 kg:
- The recommended dose of Simponi for children 2 years of age and older weighing at least 15 kg depends on their weight. Your doctor will tell you the correct dose.
- For children with a body weight of at least 15 kg with ulcerative colitis, a 50 mg pre-filled syringe or 100 mg pre-filled syringe is available. For the 50 mg dose, see section 3 “How to use Simponi” of the Simponi 50 mg pre-filled syringe package leaflet. For the 100 mg dose, see section 3 “How to use Simponi” of the Simponi 100 mg pre-filled syringe package leaflet.

How Simponi is given

- Simponi is given by injection under the skin (subcutaneously).
- At the start, your doctor or nurse may inject Simponi. However, you and your doctor may decide that you may inject Simponi to yourself or to your child. In this case you will get training on how to inject Simponi.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed “Instructions for Use” included with this leaflet.

If you use more Simponi than you should
If you have used or been given too much Simponi (either by injecting too much on a single occasion, or by using it too often), talk to your doctor or pharmacist straight away. Always take the outer carton and this leaflet with you, even if it is empty.

If you forget to use Simponi
If you forget to use Simponi on your planned date, inject the forgotten dose as soon as you remember.

Do not use a double dose to make up for a forgotten dose.

When to inject your next dose:

- If you are less than 2 weeks late, inject the forgotten dose as soon as you remember and stay on your original schedule.

- If you are more than 2 weeks late, inject the forgotten dose as soon as you remember and talk to your doctor or pharmacist to ask when you need to take the next dose.

If you are not sure what to do, talk to your doctor or pharmacist.

If you stop using Simponi
If you are considering stopping Simponi, talk to your doctor or pharmacist first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some patients may experience serious side effects and may require treatment. Side effects may appear up to several months after the last injection.

Tell your doctor straight away if you notice any of the following serious side effects of Simponi which include:
- **allergic reactions which may be serious, or rarely, life-threatening (rare).** Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions occurred after the first administration of Simponi.
- **serious infections (including TB, bacterial infections including serious blood infections and pneumonia, severe fungal infections and other opportunistic infections) (common).** Symptoms of an infection can include fever, tiredness, (persistent) cough, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.
- **reactivation of hepatitis B virus if you are a carrier or have had hepatitis B before (rare).** Symptoms can include yellowing of the skin and eyes, dark brown-coloured urine, right-sided abdominal pain, fever, feeling sick, being sick, and feeling very tired.
- **nervous system disease such as multiple sclerosis (rare).** Symptoms of nervous system disease can include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.
- **cancer of the lymph nodes (lymphoma) (rare).** Symptoms of lymphoma can include swelling of the lymph nodes, weight loss, or fever.
- **heart failure (rare).** Symptoms of heart failure can include shortness of breath or swelling of your feet.
- **signs of immune system disorders called:**
  - **lupus (rare).** Symptoms can include joint pain or a rash on cheeks or arms that is sensitive to the sun.
  - **sarcoidosis (rare).** Symptoms can include a persistent cough, being short of breath, chest pain, fever, swelling of your lymph nodes, weight loss, skin rashes, and blurred vision.
- **swelling of small blood vessels (vasculitis) (rare).** Symptoms can include fever, headache, weight loss, night sweats, rash, and nerve problems such as numbness and tingling.
- **skin cancer (uncommon).** Symptoms of skin cancer can include changes in the appearance of your skin or growths on your skin.
- **blood disease (common).** Symptoms of blood disease can include a fever that does not go away, bruising or bleeding very easily or looking very pale.
- **blood cancer (leukaemia) (rare)**. Symptoms of leukaemia can include fever, feeling tired, frequent infections, easy bruising, and night sweats.

Tell your doctor straight away if you notice any of the above symptoms.

The following additional side effects have been observed with Simponi:
Very common side effects (may affect more than 1 in 10 people):
- Upper respiratory tract infections, sore throat or hoarseness, runny nose

Common side effects (may affect up to 1 in 10 people):
- Abnormal liver tests (increased liver enzymes) found during blood tests done by your doctor
- Feeling dizzy
- Headache
- Feeling numb or having a tingling feeling
- Superficial fungal infections
- Abscess
- Bacterial infections (such as cellulitis)
- Low red blood cell counts
- Low white blood cell counts
- Positive blood lupus test
- Allergic reactions
- Indigestion
- Stomach pain
- Feeling sick (nausea)
- Flu
- Bronchitis
- Sinus infection
- Cold sores
- High blood pressure
- Fever
- Asthma, shortness of breath, wheezing
- Stomach and bowel disorders which include inflammation of the stomach lining and colon which may cause fever
- Pain and ulcers in the mouth
- Injection site reactions (including redness, hardness, pain, bruising, itching, tingling and irritation)
- Hair loss
- Rash and itching of the skin
- Difficulty sleeping
- Depression
- Feeling weak
- Bone fractures
- Chest discomfort

Uncommon side effects (may affect up to 1 in 100 people):
- Kidney infection
- Cancers, including skin cancer and non-cancerous growths or lumps, including skin moles
- Skin blisters
- Severe infection throughout the body (sepsis), sometimes including low blood pressure (septic shock)
- Psoriasis (including on the palms of your hand and/or the soles of your feet and/or in the form of skin blisters)
- Low platelet count
- Combined low platelet, red, and white blood cell count
- Thyroid disorders
- Increase in blood sugar levels
- Increase in blood cholesterol levels
- Balance disorders
- Vision disturbances

- Inflamed eye (conjunctivitis)
- Eye allergy
- Sensation of heart beating irregularly
- Narrowing of the blood vessels in the heart
- Blood clots
- Flushing
- Constipation
- Chronic inflammatory condition of the lungs
- Acid reflux
- Gall stones
- Liver disorders
- Breast disorders
- Menstrual disorders

Rare side effects (may affect up to 1 in 1,000 people):
- Failure of the bone marrow to produce blood cells
- Severely decreased number of white blood cells
- Infection of the joints or the tissue around them
- Impaired healing
- Inflammation of blood vessels in internal organs
- Leukaemia
- Melanoma (a type of skin cancer)
- Merkel cell carcinoma (a type of skin cancer)
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes)
- Scaly, peeling skin
- Immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- Pain and discolouration in the fingers or toes
- Taste disturbances
- Bladder disorders
- Kidney disorders
- Inflammation of the blood vessels in your skin which results in rash

Side effects of which the frequency is not known:
- A rare blood cancer affecting mostly young people (hepatosplenic T-cell lymphoma)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Simponi

- 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 label and 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.
- Keep the pre-filled pen in the outer carton in order to protect it from light.

- This medicine can also be stored out of the refrigerator at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not beyond the original expiry date printed on the carton. Write the new expiry date on the carton including day/month/year (no more than 30 days after the medicine is removed from the refrigerator). Do not return this medicine to refrigerator if it has reached room temperature. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not use this medicine if you notice that the liquid is not a clear to light yellow colour, cloudy, or contains foreign particles.
- Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Simponi contains
The active substance is golimumab. One 0.45 mL pre-filled pen contains 45 mg of golimumab. 1 mL contains 100 mg golimumab.

The other ingredients are sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433) and water for injections. For more information on sorbitol (E420) and polysorbate 80 (E433), see Section 2.

What Simponi looks like and contents of the pack
Simponi is supplied as solution for injection in a single-use pre-filled pen, VarioJect. Simponi is available in packs containing 1 pre-filled pen.

The solution is clear to slightly opalescent (having a pearl-like shine), colourless to light yellow and may contain a few small translucent or white particles of protein. Do not use Simponi if the solution is discoloured, cloudy or you can see foreign particles in it.

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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Instructions for Use
Simponi 45 mg/0.45 mL
solution for injection in pre-filled pen, VarioJect
For paediatric use

SINGLE-USE



Know your dose
Use the space above to record your prescribed dose.
Confirm with your doctor if you are unsure of your dose.

Important
If your doctor decides that you or a caregiver may be able to give your injections of Simponi at home, you should receive training on the right way to prepare and inject Simponi.

Please read this Instructions for Use before using the Simponi pre-filled pen and each time you get a new pre-filled pen. There may be new information.

Please also read the 'Package Leaflet: Information for the user' carefully before starting your injection. This instruction guide does not take the place of talking with your doctor about your medical condition or your treatment.

If you have not been trained, or have any questions, please contact your doctor, nurse or pharmacist.

Storage information
Store in refrigerator at 2 ° to 8 °C.

Can be stored at room temperature (up to 25 °C) for a single period up to 30 days, but not exceeding the original expiry date. Write the new expiry date on the back panel of the carton including day/month/year (no more than 30 days after the medicine is removed from the refrigerator). Do not return this medicine to refrigerator if it has reached room temperature.

Keep Simponi pre-filled pen and all medicines out of the sight and reach of children.

Overview
The pre-filled pen is a **manual** injection pen that allows you to set a specific, prescribed dose. Each pre-filled pen can deliver 0.1 mL to 0.45 mL (corresponding to 10 mg to 45 mg golimumab) in increments of 0.05 mL.

Before you begin using this pre-filled pen, you should know how to:
- Remove air bubbles
- Set prescribed dose
- **Manually press the plunger** to inject, like a syringe

The pre-filled pen is to be used only one time. Dispose of the pre-filled pen after use.

Do not attempt to use any leftover medicine in the pre-filled pen.

Do not share the pre-filled pen with anyone.

Do not shake.

Need help?
Call your doctor, nurse or pharmacist to talk about any questions you may have. For additional assistance refer to the Package Leaflet for your local representative contact information.

Plan ahead



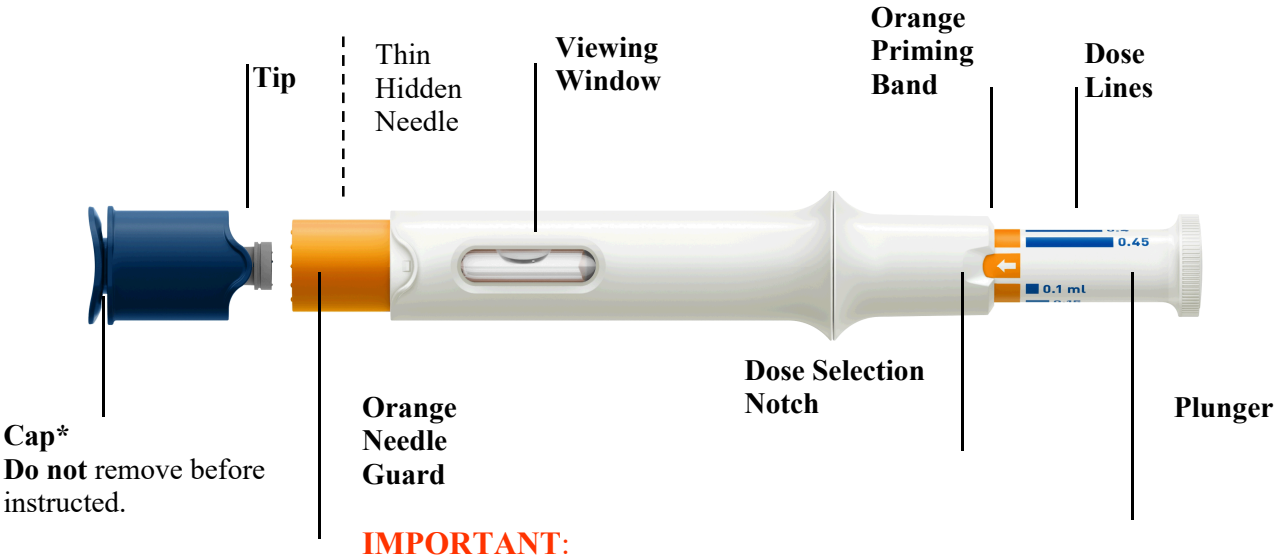
Inspect carton
Check the expiry date ("EXP") printed or written on the back panel of the carton.
Do not use if the expiry date has passed.
Do not inject if the perforations on the carton are broken. Call your doctor or pharmacist for a new pre-filled pen.



Remove the pre-filled pen from the carton
Let the pre-filled pen sit **at room temperature for at least 30 minutes** out of reach of children.
Do not warm any other way.

You will need these supplies:
- **1 Alcohol swab**
- **1 Cotton ball** or **gauze pad**
- **1 Adhesive bandage**
- **1 Sharps container** (See Step 3)

Your pre-filled pen at-a-glance



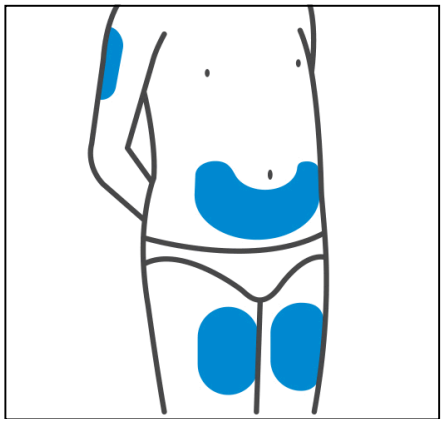
IMPORTANT:

Do not press on the orange needle guard before the injection. It will lock, and you will not receive the dose.

Do not lift the pre-filled pen from the skin during the injection. The orange needle guard will lock, and you will not receive the full dose.

*CHOKING HAZARD! Keep out of reach of children.

1. Prepare for your injection



Choose injection site

Select from the following areas for your injection:

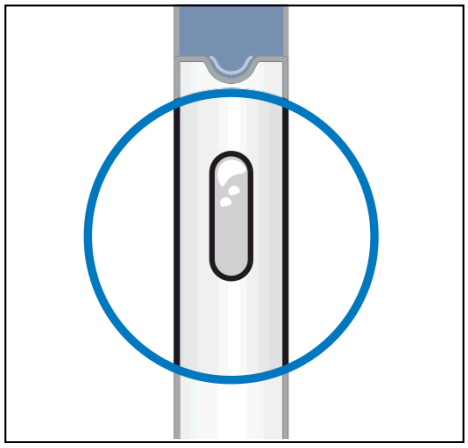
- **Front of thighs** (recommended)
- Lower abdomen
  Do not use the 5-centimetre area around your belly-button.
- Back of upper arms (if a caregiver is giving you the injection)

Choose a different site within your preferred area for each injection.

Do not inject into skin that is tender, bruised, red, scaly, hard or has scars.

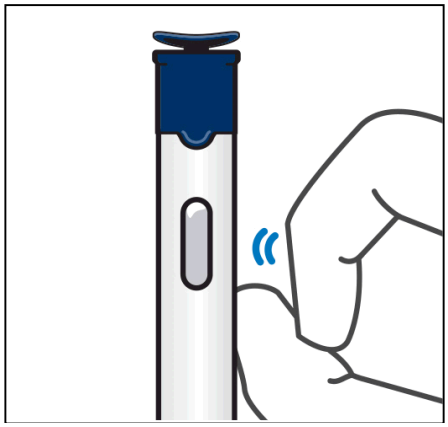


Clean injection site
Wash your hands well with soap and warm water.
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan, or blow on the injection site after you have cleaned it.



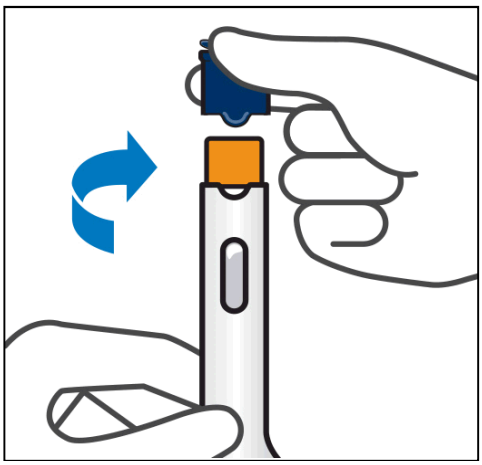
Inspect liquid
Take the pre-filled pen out of the carton.
Check the liquid in the viewing window. It should be clear to slightly opalescent (having pearl-like shine) and colourless to light yellow and may contain a few small translucent or white particles of protein. You may also see one or more air bubbles. This is normal.

Do not inject if the liquid is the wrong colour, cloudy or has large particles. If you are uncertain, call your doctor or pharmacist for a new pre-filled pen.



Tap air bubbles to top
Hold the pre-filled pen upright with the blue cap pointing up.

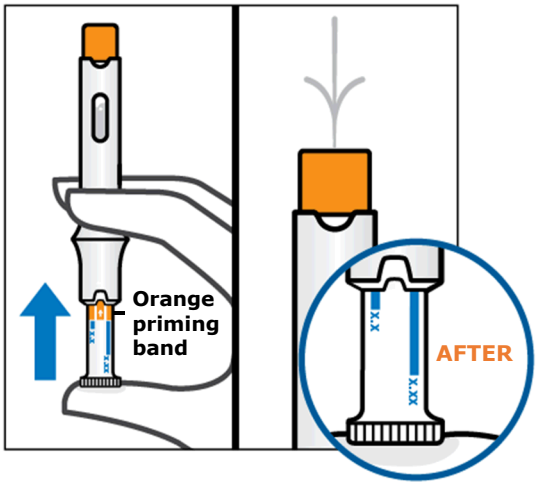
Tap the pre-filled pen gently with your finger near the viewing window. This will cause any air bubbles to rise to the top.



Remove cap
Keep holding the pre-filled pen upright, then twist and pull the cap to remove.

IMPORTANT: Do not press on the orange needle guard before the injection. It will lock, and you will not receive the dose.

Inject within 5 minutes of removing the cap.
Do not put the cap back on, this may damage the hidden needle.
Do not use the pre-filled pen if it is dropped without the cap on.
Call your doctor or pharmacist for a new pre-filled pen.

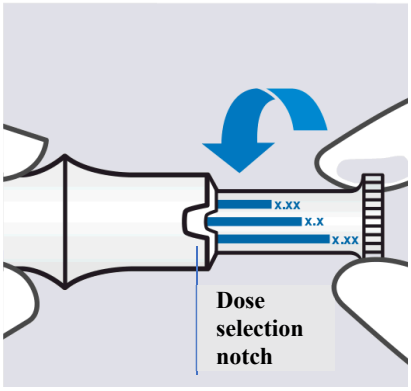


Remove air bubbles*
Keep holding the pre-filled pen upright.
Gently, press the plunger up with your thumb until it stops. Liquid will squirt out. This is normal.

The orange priming band will disappear.

**Removing air bubbles helps make sure the right dose is given.*
After you remove the air bubbles, you may see a line inside the viewing window. This is normal.

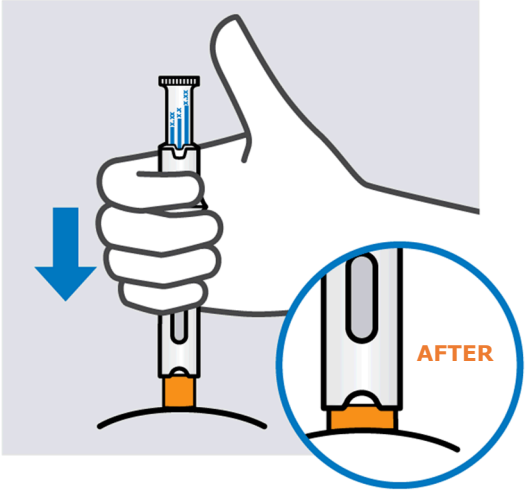
2. Inject Simponi using the pre-filled pen



Set prescribed dose
Turn plunger until the dose line for your prescribed dose lines up with the dose selection notch. The pre-filled pen is now ready to use.

Dose selections:

- 0.1 mL
- 0.15 mL
- 0.2 mL
- 0.25 mL
- 0.3 mL
- 0.35 mL
- 0.4 mL
- 0.45 mL

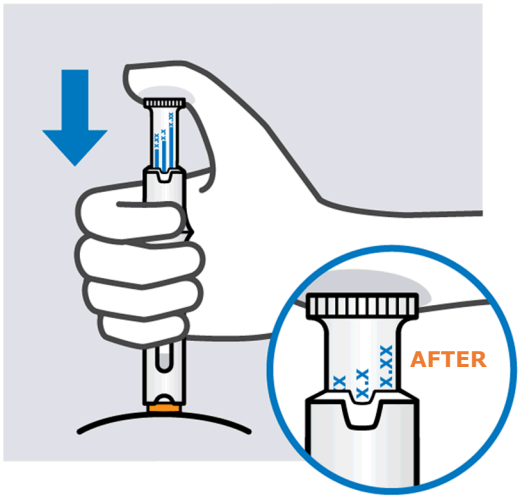


Insert needle and hold in place

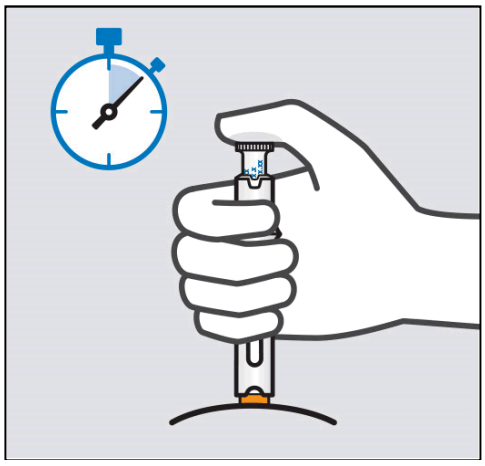
IMPORTANT: Do not lift the pre-filled pen from the skin during the injection. The orange needle guard will lock, and you will not receive the full dose.

Do not press the plunger while inserting the needle.

Push and hold the pre-filled pen tip against the skin so the orange needle guard pushes up until it stops. Some orange will still be showing.

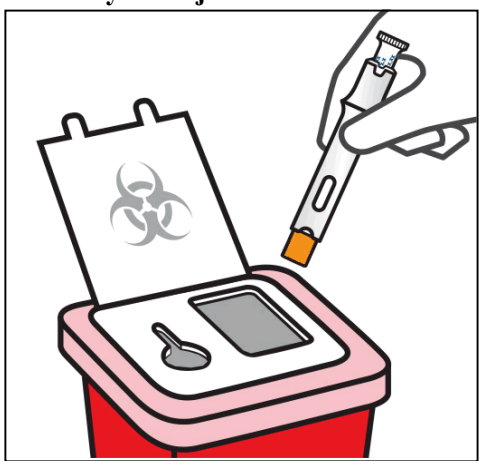


Inject Simponi
Keep pushing the pre-filled pen against the skin.
Gently, press the plunger until it stops.
If a small dose is set, the plunger will only move a short distance.
The dose you delivered can be confirmed by viewing the dose selection notch.
Do not lift the pre-filled pen up yet.

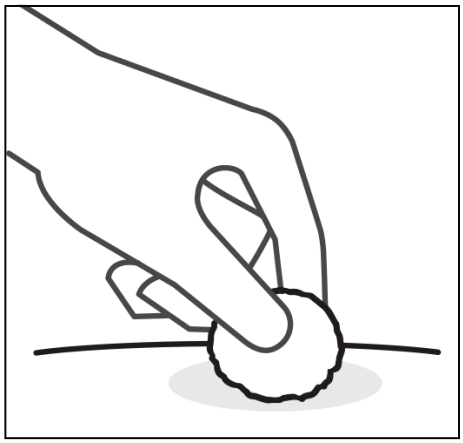


Keep holding, then lift
Keep pushing the pre-filled pen against the skin for approximately 5 seconds.
It is normal to see some drug still visible in the viewing window.
Lift the pre-filled pen away from the skin.
The orange needle guard will extend and lock.

3. After your injection



Throw the used pre-filled pen away
Put your used pre-filled pen in a sharps disposal container right away after use.
Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.



Check injection site
There may be a small amount of blood or liquid at the injection site.
Hold pressure on your skin with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site.
If needed, cover injection site with a bandage. Your injection is now complete!

Package Leaflet: Information for the user

Simponi 50 mg solution for injection in pre-filled pen
golimumab

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.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

Your doctor will also give you a Patient Card, which contains important safety information you need to be aware of before and during your treatment with Simponi.

What is in this leaflet

1. What Simponi is and what it is used for
2. What you need to know before you use Simponi
3. How to use Simponi
4. Possible side effects
5. How to store Simponi
6. Contents of the pack and other information

1. What Simponi is and what it is used for

Simponi contains the active substance called golimumab.

Simponi belongs to a group of medicines called 'TNF blockers'. It is used **in adults** for the treatment of the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis
- Ulcerative colitis

In children 2 years of age and older, Simponi is used for the treatment of polyarticular juvenile idiopathic arthritis.

Simponi works by blocking the action of a protein called 'tumour necrosis factor alpha' (TNF-α). This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body.

Rheumatoid arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi which you will take in combination with another medicine called methotrexate to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis, an inflammatory disease of the skin. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Ankylosing spondylitis and non-radiographic axial spondyloarthritis
Ankylosing spondylitis and non-radiographic axial spondyloarthritis are inflammatory diseases of the spine. If you have ankylosing spondylitis or non-radiographic axial spondyloarthritis, you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simponi to treat your disease.

Polyarticular juvenile idiopathic arthritis
Polyarticular juvenile idiopathic arthritis is an inflammatory disease that causes joint pain and swelling in children. If you have polyarticular juvenile idiopathic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simponi in combination with methotrexate to treat the disease.

2. What you need to know before you use Simponi

Do not use Simponi
- If you are allergic (hypersensitive) to golimumab or any of the other ingredients of this medicine (listed in Section 6).
- If you have tuberculosis (TB) or any other severe infection.
- If you have moderate or severe heart failure.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Simponi.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Simponi.

Infections
Tell your doctor straight away if you already have or get any symptoms of infection, during or after your treatment with Simponi. Symptoms of infection include fever, cough, shortness of breath, flu-like symptoms, diarrhoea, wounds, dental problems or a burning feeling when urinating.
- You may get infections more easily while using Simponi.
- Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

Tuberculosis (TB)
Tell your doctor straight away if symptoms of TB appear during or after your treatment. Symptoms of TB include persistent cough, weight loss, tiredness, fever or night sweats.
- Cases of TB have been reported in patients treated with Simponi, in rare occasions even in patients who have been treated with medicines for TB. Your doctor will test you to see if you have TB. Your doctor will record these tests on your Patient Card.

- It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had or has TB.
- If your doctor feels that you are at risk of TB, you may be treated with medicines for TB before you begin using Simponi.

Hepatitis B virus (HBV)
- Tell your doctor if you are a carrier or if you have or have had HBV before you are given Simponi.
- Tell your doctor if you think you might be at risk of contracting HBV
- Your doctor should test you for HBV
- Treatment with TNF blockers such as Simponi may result in reactivation of HBV in patients who carry this virus, which can be life-threatening in some cases.

Invasive fungal infections
If you have lived in or travelled to an area where infections caused by specific type of fungi that can affect the lungs or other parts of the body (called histoplasmosis, coccidioidomycosis, or blastomycosis), are common, tell your doctor straight away. Ask your doctor if you don't know if these fungal infections are common in the area in which you have lived or travelled.

Cancer and lymphoma
Tell your doctor if you have ever been diagnosed with lymphoma (a type of blood cancer) or any other cancer before you use Simponi.
- If you use Simponi or other TNF blockers, your risk for developing lymphoma or another cancer may increase.
- Patients with severe rheumatoid arthritis and other inflammatory diseases, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
- There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death.
- On rare occasions, a specific and severe type of lymphoma called hepatosplenic T-cell lymphoma has been observed in patients taking other TNF-blockers. Most of these patients were adolescent or young adult males. This type of cancer has usually resulted in death. Almost all of these patients had also received medicines known as azathioprine or 6-mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Simponi.
- Patients with severe persistent asthma, chronic obstructive pulmonary disease (COPD), or are heavy smokers may be at increased risk for cancer with Simponi treatment. If you have severe persistent asthma, COPD or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.
- Some patients treated with golimumab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Heart failure
Tell your doctor straight away if you get new or worsening symptoms of heart failure. Symptoms of heart failure include shortness of breath or swelling of your feet.
- New and worsening congestive heart failure has been reported with TNF blockers, including Simponi. Some of these patients died.
- If you have mild heart failure and you are being treated with Simponi, you must be closely monitored by your doctor.

Nervous system disease
Tell your doctor straight away if you have ever been diagnosed with or develop symptoms of a demyelinating disease such as multiple sclerosis. Symptoms may include changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body. Your doctor will decide if you should receive Simponi.

Operations or dental procedures
- Talk to your doctor if you are going to have any operations or dental procedures.
- Tell your surgeon or dentist performing the procedure that you are having treatment with Simponi by showing them your Patient Card.

Autoimmune disease
Tell your doctor if you develop symptoms of a disease called lupus. Symptoms include persistent rash, fever, joint pain and tiredness.
- On rare occasions, people treated with TNF blockers have developed lupus.

Blood disease
In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Vaccinations
Talk to your doctor if you have had, or are due to have a vaccine.
- You should not receive certain (live) vaccines while using Simponi.
- Certain vaccinations may cause infections. If you received Simponi while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Simponi use so they can decide when your baby should receive any vaccine.

Talk to your child's doctor regarding vaccinations for your child. If possible, your child should be up to date with all vaccinations before using Simponi.

Therapeutic infectious agents
Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Allergic reactions
Tell your doctor straight away if you develop symptoms of an allergic reaction after your treatment with Simponi. Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles.
- Some of these reactions may be serious or, rarely, life-threatening.
- Some of these reactions occurred after the first administration of Simponi.

Children
Simponi is not recommended for children less than 2 years of age with polyarticular juvenile idiopathic arthritis because it has not been studied in this group.

Other medicines and Simponi
- Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including any other medicines to treat rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis.
- You should not take Simponi with medicines containing the active substance anakinra or abatacept. These medicines are used for the treatment of rheumatic diseases.
- Tell your doctor or pharmacist if you are taking any other medicines that affect your immune system.
- You should not receive certain (live) vaccines while using Simponi.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Pregnancy and breast-feeding
Talk to your doctor before using Simponi if:
- You are pregnant or are planning to become pregnant while using Simponi. There is limited information about the effects of this medicine in pregnant women. If you are being treated with Simponi, you must avoid becoming pregnant by using adequate contraception during your treatment and for at least 6 months after the last Simponi injection. Simponi should only be used during pregnancy if it is clearly necessary for you.
- Before starting breast-feeding, your last treatment with Simponi must be at least 6 months ago. You must stop breast-feeding if you are to be given Simponi.
- If you received Simponi during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Simponi use before the baby receives any vaccine (for more information see section on vaccination).

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Simponi has minor influence on your ability to drive and use tools or machines. Dizziness may however occur after you take Simponi. If this happens, do not drive or use any tools or machines.

Simponi contains latex, sorbitol and polysorbate
Latex sensitivity
A part of the pre-filled pen, the needle cover, contains latex. Because latex may cause severe allergic reactions, talk to your doctor before using Simponi if you or your carer are allergic to latex.

Sorbitol intolerance
This medicine contains 20.5 mg sorbitol (E420) in each pre-filled pen.

Polysorbate 80
This medicine contains 0.075 mg of polysorbate 80 (E433) in each pre-filled pen. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Simponi

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

How much Simponi is given
Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis:
- The recommended dose is 50 mg (the content of 1 pre-filled pen) given once a month, on the same date each month.
- Talk to your doctor before taking your fourth dose. Your doctor will determine if you should continue Simponi treatment.
    - If you weigh more than 100 kg, the dose might be increased to 100 mg (the content of 2 pre-filled pens) given once a month, on the same date each month.

Polyarticular juvenile idiopathic arthritis in children 2 years of age and older:
- For patients weighing at least 40 kg, the recommended dose is 50 mg given once a month, on the same date each month. For patients weighing less than 40 kg, a 45 mg/0.45 mL pre-filled pen is available. Your doctor will tell you the correct dose to use.

- Talk to your doctor before you take the fourth dose. Your doctor will determine if you should continue Simponi treatment.

Ulcerative colitis
- The table below shows how you will usually use this medicine.

Initial treatment	A starting dose of 200 mg (the contents of 4 pre-filled pens) followed by 100 mg (the contents of 2 pre-filled pens) 2 weeks later.
Maintenance treatment	• In patients weighing less than 80 kg, 50 mg (the contents of 1 pre-filled pen) 4 weeks after your last treatment, then every 4 weeks thereafter. Your doctor may decide to prescribe 100 mg (the contents of 2 pre-filled pens), depending on how well Simponi works for you. • In patients weighing 80 kg or more, 100 mg (the contents of 2 pre-filled pens) 4 weeks after your last treatment, then every 4 weeks thereafter.

How Simponi is given
- Simponi is given by injection under the skin (subcutaneously).
- At the start, your doctor or nurse may inject Simponi. However, you and your doctor may decide that you may inject Simponi yourself. In this case you will get training on how to inject Simponi yourself.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed "Instructions for Use" at the end of this leaflet.

If you use more Simponi than you should
If you have used or been given too much Simponi (either by injecting too much on a single occasion, or by using it too often), talk to your doctor or pharmacist straight away. Always take the outer carton and this leaflet with you, even if it is empty.

If you forget to use Simponi
If you forget to use Simponi on your planned date, inject the forgotten dose as soon as you remember.

Do not use a double dose to make up for a forgotten dose.

When to inject your next dose:
- If you are less than 2 weeks late, inject the forgotten dose as soon as you remember and stay on your original schedule.
- If you are more than 2 weeks late, inject the forgotten dose as soon as you remember and talk to your doctor or pharmacist to ask when you need to take the next dose.

If you are not sure what to do, talk to your doctor or pharmacist.

If you stop using Simponi
If you are considering stopping Simponi, talk to your doctor or pharmacist first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some patients may experience serious side effects and may require treatment. The risk of certain side effects is greater with the 100 mg dose compared with the 50 mg dose. Side effects may appear up to several months after the last injection.

Tell your doctor straight away if you notice any of the following serious side effects of Simponi which include:

- **allergic reactions which may be serious, or rarely, life-threatening (rare).** Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions occurred after the first administration of Simponi.
- **serious infections (including TB, bacterial infections including serious blood infections and pneumonia, severe fungal infections and other opportunistic infections) (common).** Symptoms of an infection can include fever, tiredness, (persistent) cough, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.
- **reactivation of hepatitis B virus if you are a carrier or have had hepatitis B before (rare).** Symptoms can include yellowing of the skin and eyes, dark brown-coloured urine, right-sided abdominal pain, fever, feeling sick, being sick, and feeling very tired.
- **nervous system disease such as multiple sclerosis (rare).** Symptoms of nervous system disease can include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.
- **cancer of the lymph nodes (lymphoma) (rare).** Symptoms of lymphoma can include swelling of the lymph nodes, weight loss, or fever.
- **heart failure (rare).** Symptoms of heart failure can include shortness of breath or swelling of your feet.
- **signs of immune system disorders called:**
  - **lupus (rare).** Symptoms can include joint pain or a rash on cheeks or arms that is sensitive to the sun.
  - **sarcoidosis (rare).** Symptoms can include a persistent cough, being short of breath, chest pain, fever, swelling of your lymph nodes, weight loss, skin rashes, and blurred vision.
- **swelling of small blood vessels (vasculitis) (rare).** Symptoms can include fever, headache, weight loss, night sweats, rash, and nerve problems such as numbness and tingling.
- **skin cancer (uncommon).** Symptoms of skin cancer can include changes in the appearance of your skin or growths on your skin.
- **blood disease (common).** Symptoms of blood disease can include a fever that does not go away, bruising or bleeding very easily or looking very pale.
- **blood cancer (leukaemia) (rare)**. Symptoms of leukaemia can include fever, feeling tired, frequent infections, easy bruising, and night sweats.

Tell your doctor straight away if you notice any of the above symptoms.

The following additional side effects have been observed with Simponi:

<u>Very common side effects (may affect more than 1 in 10 people):</u>

- Upper respiratory tract infections, sore throat or hoarseness, runny nose

<u>Common side effects (may affect up to 1 in 10 people):</u>

- Abnormal liver tests (increased liver enzymes) found during blood tests done by your doctor
- Feeling dizzy
- Headache
- Feeling numb or having a tingling feeling
- Superficial fungal infections
- Abscess
- Bacterial infections (such as cellulitis)
- Low red blood cell counts
- Low white blood cell counts
- Positive blood lupus test
- Allergic reactions
- Indigestion
- Stomach pain
- Feeling sick (nausea)

- Flu
- Bronchitis
- Sinus infection
- Cold sores
- High blood pressure
- Fever
- Asthma, shortness of breath, wheezing
- Stomach and bowel disorders which include inflammation of the stomach lining and colon which may cause fever
- Pain and ulcers in the mouth
- Injection site reactions (including redness, hardness, pain, bruising, itching, tingling and irritation)
- Hair loss
- Rash and itching of the skin
- Difficulty sleeping
- Depression
- Feeling weak
- Bone fractures
- Chest discomfort

Uncommon side effects (may affect up to 1 in 100 people):
- Kidney infection
- Cancers, including skin cancer and non-cancerous growths or lumps, including skin moles
- Skin blisters
- Severe infection throughout the body (sepsis), sometimes including low blood pressure (septic shock)
- Psoriasis (including on the palms of your hand and/or the soles of your feet and/or in the form of skin blisters)
- Low platelet count
- Combined low platelet, red, and white blood cell count
- Thyroid disorders
- Increase in blood sugar levels
- Increase in blood cholesterol levels
- Balance disorders
- Vision disturbances
- Inflamed eye (conjunctivitis)
- Eye allergy
- Sensation of heart beating irregularly
- Narrowing of the blood vessels in the heart
- Blood clots
- Flushing
- Constipation
- Chronic inflammatory condition of the lungs
- Acid reflux
- Gall stones
- Liver disorders
- Breast disorders
- Menstrual disorders

Rare side effects (may affect up to 1 in 1,000 people):
- Failure of the bone marrow to produce blood cells
- Severely decreased number of white blood cells
- Infection of the joints or the tissue around them
- Impaired healing

- Inflammation of blood vessels in internal organs
- Leukaemia
- Melanoma (a type of skin cancer)
- Merkel cell carcinoma (a type of skin cancer)
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes)
- Scaly, peeling skin
- Immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- Pain and discolouration in the fingers or toes
- Taste disturbances
- Bladder disorders
- Kidney disorders
- Inflammation of the blood vessels in your skin which results in rash

Side effects of which the frequency is not known:
- A rare blood cancer affecting mostly young people (hepatosplenic T-cell lymphoma)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Simponi

- 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 label and 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.
- Keep the pre-filled pen in the outer carton in order to protect it from light.
- This medicine can also be stored out of the refrigerator at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not beyond the original expiry date printed on the carton. Write the new expiry date on the carton including day/month/year (no more than 30 days after the medicine is removed from the refrigerator). Do not return this medicine to refrigerator if it has reached room temperature. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not use this medicine if you notice that the liquid is not a clear to light yellow colour, cloudy, or contains foreign particles.
- Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Simponi contains
The active substance is golimumab. One 0.5 mL pre-filled pen contains 50 mg of golimumab.

The other ingredients are sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433) and water for injections. For more information on sorbitol (E420) and polysorbate 80 (E433), see Section 2.

What Simponi looks like and contents of the pack
Simponi is supplied as solution for injection in a single-use pre-filled pen. Simponi is available in packs containing 1 pre-filled pen and multipacks containing 3 (3 packs of 1) pre-filled pens. Not all pack sizes may be marketed.

The solution is clear to slightly opalescent (having a pearl-like shine), colourless to light yellow and may contain a few small translucent or white particles of protein. Do not use Simponi if the solution is discoloured, cloudy or you can see foreign particles in it.

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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

If you would like to self inject Simponi, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your doctor, nurse or pharmacist to schedule a training session.

In these instructions:
1. Preparing for use of the pre-filled pen
2. Choosing and preparing the injection site
3. Injecting the medicine
4. After the injection

The diagram below (see figure 1) shows what the "SmartJect" pre-filled pen looks like.

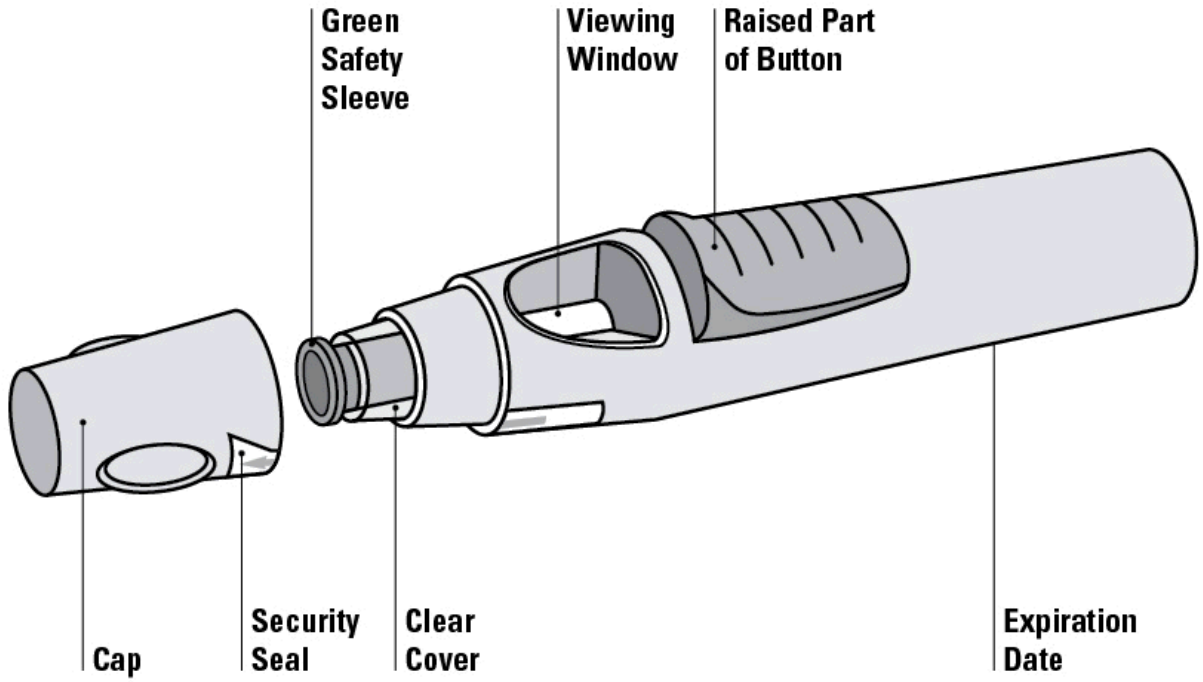


Figure 1

1. Preparing for use of the pre-filled pen

- Do not shake the pre-filled pen at any time.
- Do not remove the cap from the pre-filled pen until immediately before the injection.
- Do not put the cap of the pre-filled pen back on if removed to avoid bending the needle.

Check the number of pre-filled pens
Check the pre-filled pens to make sure
- the number of pre-filled pens and strength is correct
    - If your dose is 50 mg, you will get one 50 mg pre-filled pen
    - If your dose is 100 mg, you will get two 50 mg pre-filled pens and you will need to give yourself two injections. Choose two different sites for these injections (e.g. one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other.
    - If your dose is 200 mg, you will get four 50 mg pre-filled pens and you will need to give yourself four injections. Choose different sites for these injections and give the injections one right after the other.

Check expiry date
- Check the expiry date printed or written on the carton.
- Check the expiry date (as indicated as "EXP") on the pre-filled pen.
- Do not use the pre-filled pen if the expiry date has passed. The printed expiry date refers to the last day of the month. Please contact your doctor or pharmacist for assistance.

Check security seal
- Check the security seal around the cap of the pre-filled pen.
- Do not use the pre-filled pen if the seal is broken. Please contact your doctor or pharmacist.

Wait 30 minutes to allow pre-filled pen to reach room temperature
- To ensure proper injection, allow the pre-filled pen to sit at room temperature outside the box for 30 minutes out of the reach of children.
- Do not warm the pre-filled pen in any other way (for example, do not warm it in a microwave or in hot water).
- Do not remove the pre-filled pen's cap while allowing it to reach room temperature.

Get the rest of your equipment ready
- While you are waiting you can get the rest of your equipment ready, including an alcohol swab, a cotton ball or gauze and a sharps container.

Check the liquid in the pre-filled pen
- Look through the viewing window to make sure that the liquid in the pre-filled pen is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow. The solution can be used if it contains a few small translucent or white particles of protein.
- You will also notice an air bubble, which is normal.
- Do not use the pre-filled pen if the liquid is the wrong colour, cloudy, or contains larger particles. If this happens, talk to your doctor or pharmacist.

2. Choosing and preparing the injection site (see figure 2)

- You can inject the medicine into the front of the middle thighs.
- You can use the stomach (abdomen) below the belly button, except for approximately the 5 cm area directly underneath the belly button.
- Do not inject into areas where the skin is tender, bruised, red, scaly, hard or has scars or stretch marks.
- If multiple injections are required for a single administration, the injections should be administered at different injection sites.

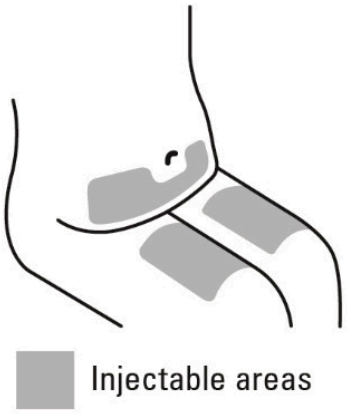


Figure 2

⚠ **DO NOT** inject into the arm to avoid failure of the pre-filled pen and/or unintentional injury.

Wash hands and clean the injection site

- Wash your hands thoroughly with soap and warm water.
- Wipe the injection site with an alcohol swab.
- Allow the skin to dry before injecting. Do not fan or blow on the clean area.
- Do not touch this area again before giving the injection.

3. Injecting the medicine

- The cap should not be removed until you are ready to inject the medicine.
- The medicine should be injected within 5 minutes after the cap has been removed.

Remove the cap (figure 3)

- When you are ready to inject, twist the cap slightly to break the security seal.
- Pull the cap off and throw it away after your injection.
- Do not put the cap back on because it may damage the needle inside the pre-filled pen.
- Do not use the pre-filled pen if it is dropped without the cap in place. If this happens please contact your doctor or pharmacist.

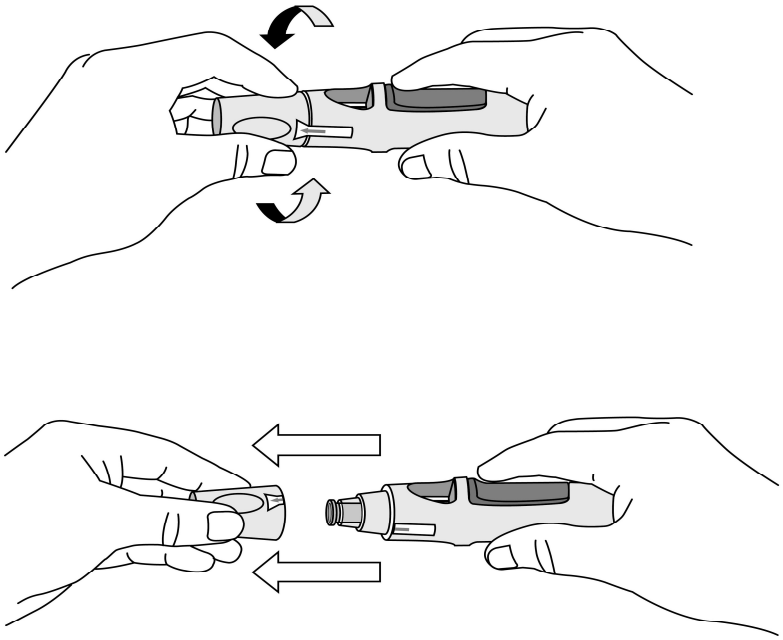


Figure 3

Push the pre-filled pen against the skin (see figures 4 and 5) without pinching the skin.

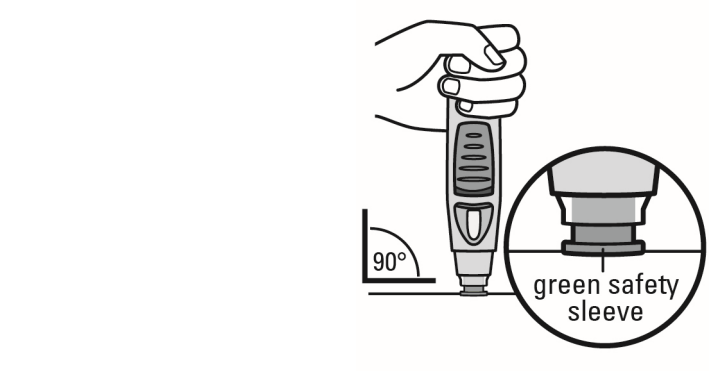


Figure 4

- Hold the pre-filled pen comfortably with one hand **above the blue button**.
- Make sure the green safety sleeve is stable and is as flat as possible against your skin. If the pre-filled pen is not stable during the injection, you risk bending the needle.
- DO NOT pinch the skin to avoid unintentional needlestick injury.
- DO NOT touch or press the blue button while positioning the pre-filled pen onto your skin.

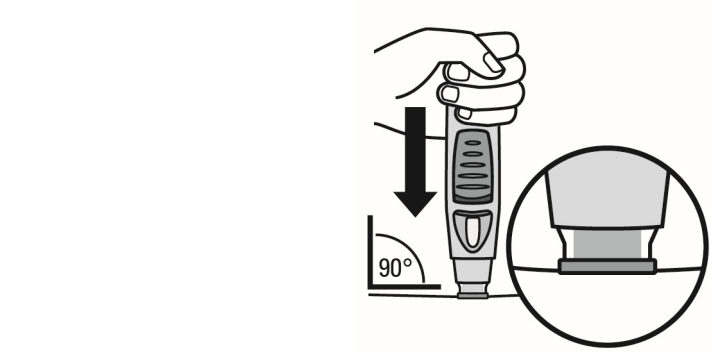


Figure 5

- Push the open end of the pre-filled pen against the skin at a 90-degree angle. Apply enough pressure to slide the green safety sleeve up and to maintain it inside the clear cover. Only the wider portion of the green safety sleeve remains outside of the clear cover.
- DO NOT press the blue button until after the safety sleeve slides into the clear cover. Pushing the blue button before the safety sleeve is depressed can lead to pen failure.
- Inject without pinching the skin.

Press button to inject (see figures 6 and 7)

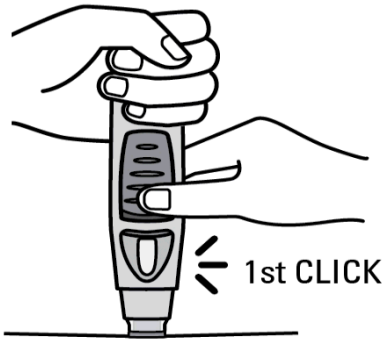


Figure 6

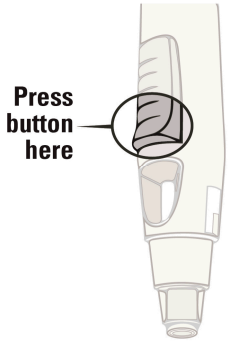


Figure 7

- Continue to push the pre-filled pen against your skin. **Use your other hand** to press the **raised part of the blue button** to start your injection. Do not press the button unless the pre-filled pen is **pressed against your skin** and the safety sleeve slides into the clear cover.
- Once the button is pressed, it will remain pressed in so you do not need to keep pressure on it.
- If the button seems hard to depress, don't press the button harder. Let go of the button, lift the pre-filled pen and start again. Ensure no pressure is on the button until the green safety sleeve is fully depressed against the skin, then press the raised part of the button.
- **You will hear a loud 'click' sound – don't be alarmed.** The first 'click' means that the needle has been inserted and the injection has started. You may or may not feel a needle prick at this time.

Do not lift the pre-filled pen away from your skin. If you pull the pre-filled pen away from your skin, you may not get your full dose of medicine.

Continue to hold until the second 'click' (see figure 8), it usually takes about 3 to 6 seconds, but may take up to 15 seconds for you to hear the second 'click' sound.

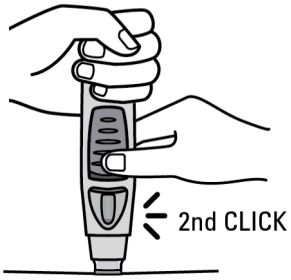


Figure 8

- **Continue to hold the pre-filled pen against your skin until you hear a second 'click' (indicating that the injection has finished and the needle has gone back into the pre-filled pen).**
- Lift the pre-filled pen from the injection site.
- Note: If you do not hear the second 'click', wait 15 seconds from the time you first press the button and then lift the autoinjector from the injection site.

4. After the injection

Use a cotton ball or gauze
- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site for 10 seconds.
- You may cover the injection site with a small adhesive bandage, if necessary.
- Do not rub your skin.

Check the window – a yellow indicator confirms proper administration (see figure 9)
- The yellow indicator is connected to the plunger of the pre-filled pen. If the yellow indicator is not shown in the window, the plunger has not advanced adequately, and the injection has not occurred.
- The yellow indicator will fill about half of the viewing window. This is normal.
- Talk to your doctor or pharmacist if the yellow indicator is not visible in the window or if you suspect that you may not have received a complete dose. Do not administer a second dose without speaking to your doctor.

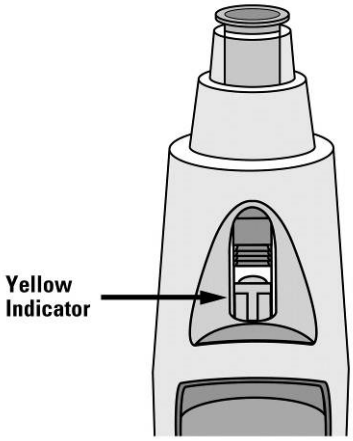


Figure 9

Throw the pre-filled pen away (see figure 10)

- Place your pen in a sharps container straight away. Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.

If you feel that something has gone wrong with the injection or if you are not sure, talk to your doctor or pharmacist.



Figure 10

Package Leaflet: Information for the user

Simponi 50 mg solution for injection in pre-filled syringe
golimumab

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.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

Your doctor will also give you a Patient Card, which contains important safety information you need to be aware of before and during your treatment with Simponi.

What is in this leaflet

1. What Simponi is and what it is used for
2. What you need to know before you use Simponi
3. How to use Simponi
4. Possible side effects
5. How to store Simponi
6. Contents of the pack and other information

1. What Simponi is and what it is used for

Simponi contains the active substance called golimumab.

Simponi belongs to a group of medicines called 'TNF blockers'. It is used **in adults** for the treatment of the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis
- Ulcerative colitis

Simponi is used **in children** 2 years of age and older for the treatment of polyarticular juvenile idiopathic arthritis and **in children** 2 years of age and older and above 15 kg for the treatment of paediatric ulcerative colitis.

Simponi works by blocking the action of a protein called 'tumour necrosis factor alpha' (TNF-α). This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body.

Rheumatoid arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi which you will take in combination with another medicine called methotrexate to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis, an inflammatory disease of the skin. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Ankylosing spondylitis and non-radiographic axial spondyloarthritis
Ankylosing spondylitis and non-radiographic axial spondyloarthritis are inflammatory diseases of the spine. If you have ankylosing spondylitis or non-radiographic axial spondyloarthritis, you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.

Ulcerative colitis (adult and paediatric)
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simponi to treat your disease.

Polyarticular juvenile idiopathic arthritis
Polyarticular juvenile idiopathic arthritis is an inflammatory disease that causes joint pain and swelling in children. If you have polyarticular juvenile idiopathic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simponi in combination with methotrexate to treat the disease.

2. What you need to know before you use Simponi

Do not use Simponi
- If you are allergic (hypersensitive) to golimumab or any of the other ingredients of this medicine (listed in Section 6).
- If you have tuberculosis (TB) or any other severe infection.
- If you have moderate or severe heart failure.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Simponi.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Simponi.

Infections
Tell your doctor straight away if you already have or get any symptoms of infection, during or after your treatment with Simponi. Symptoms of infection include fever, cough, shortness of breath, flu-like symptoms, diarrhoea, wounds, dental problems or a burning feeling when urinating.
- You may get infections more easily while using Simponi.
- Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

Tuberculosis (TB)
Tell your doctor straight away if symptoms of TB appear during or after your treatment. Symptoms of TB include persistent cough, weight loss, tiredness, fever or night sweats.
- Cases of TB have been reported in patients treated with Simponi, in rare occasions even in patients who have been treated with medicines for TB. Your doctor will test you to see if you have TB. Your doctor will record these tests on your Patient Card.

- It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had or has TB.
- If your doctor feels that you are at risk of TB, you may be treated with medicines for TB before you begin using Simponi.

Hepatitis B virus (HBV)
- Tell your doctor if you are a carrier or if you have or have had HBV before you are given Simponi.
- Tell your doctor if you think you might be at risk of contracting HBV
- Your doctor should test you for HBV
- Treatment with TNF blockers such as Simponi may result in reactivation of HBV in patients who carry this virus, which can be life-threatening in some cases.

Invasive fungal infections
If you have lived in or travelled to an area where infections caused by specific type of fungi that can affect the lungs or other parts of the body (called histoplasmosis, coccidioidomycosis, or blastomycosis), are common, tell your doctor straight away. Ask your doctor if you don't know if these fungal infections are common in the area in which you have lived or travelled.

Cancer and lymphoma
Tell your doctor if you have ever been diagnosed with lymphoma (a type of blood cancer) or any other cancer before you use Simponi.
- If you use Simponi or other TNF blockers, your risk for developing lymphoma or another cancer may increase.
- Patients with severe rheumatoid arthritis and other inflammatory diseases, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
- There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death.
- On rare occasions, a specific and severe type of lymphoma called hepatosplenic T-cell lymphoma has been observed in patients taking other TNF-blockers. Most of these patients were adolescent or young adult males. This type of cancer has usually resulted in death. Almost all of these patients had also received medicines known as azathioprine or 6-mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Simponi.
- Patients with severe persistent asthma, chronic obstructive pulmonary disease (COPD), or are heavy smokers may be at increased risk for cancer with Simponi treatment. If you have severe persistent asthma, COPD or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.
- Some patients treated with golimumab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Heart failure
Tell your doctor straight away if you get new or worsening symptoms of heart failure. Symptoms of heart failure include shortness of breath or swelling of your feet.
- New and worsening congestive heart failure has been reported with TNF blockers, including Simponi. Some of these patients died.
- If you have mild heart failure and you are being treated with Simponi, you must be closely monitored by your doctor.

Nervous system disease
Tell your doctor straight away if you have ever been diagnosed with or develop symptoms of a demyelinating disease such as multiple sclerosis. Symptoms may include changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body. Your doctor will decide if you should receive Simponi.

Operations or dental procedures
- Talk to your doctor if you are going to have any operations or dental procedures.
- Tell your surgeon or dentist performing the procedure that you are having treatment with Simponi by showing them your Patient Card.

Autoimmune disease
Tell your doctor if you develop symptoms of a disease called lupus. Symptoms include persistent rash, fever, joint pain and tiredness.
- On rare occasions, people treated with TNF blockers have developed lupus.

Blood disease
In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Vaccinations
Talk to your doctor if you have had, or are due to have a vaccine.
- You should not receive certain (live) vaccines while using Simponi.
- Certain vaccinations may cause infections. If you received Simponi while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Simponi use so they can decide when your baby should receive any vaccine.

Talk to your child's doctor regarding vaccinations for your child. If possible, your child should be up to date with all vaccinations before using Simponi.

Therapeutic infectious agents
Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Allergic reactions
Tell your doctor straight away if you develop symptoms of an allergic reaction after your treatment with Simponi. Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles.
- Some of these reactions may be serious or, rarely, life-threatening.
- Some of these reactions occurred after the first administration of Simponi.

Children
Simponi is not recommended for children less than 2 years of age with polyarticular juvenile idiopathic arthritis or paediatric ulcerative colitis because it has not been studied in these groups.

Other medicines and Simponi
- Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including any other medicines to treat rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis.
- You should not take Simponi with medicines containing the active substance anakinra or abatacept. These medicines are used for the treatment of rheumatic diseases.
- Tell your doctor or pharmacist if you are taking any other medicines that affect your immune system.
- You should not receive certain (live) vaccines while using Simponi.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Pregnancy and breast-feeding
Talk to your doctor before using Simponi if:
- You are pregnant or are planning to become pregnant while using Simponi. There is limited information about the effects of this medicine in pregnant women. If you are being treated with Simponi, you must avoid becoming pregnant by using adequate contraception during your treatment and for at least 6 months after the last Simponi injection. Simponi should only be used during pregnancy if it is clearly necessary for you.
- Before starting breast-feeding, your last treatment with Simponi must be at least 6 months ago. You must stop breast-feeding if you are to be given Simponi.
- If you received Simponi during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Simponi use before the baby receives any vaccine (for more information see section on vaccination).

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Simponi has minor influence on your ability to drive and use tools or machines. Dizziness may however occur after you take Simponi. If this happens, do not drive or use any tools or machines.

Simponi contains latex, sorbitol and polysorbate
Latex sensitivity
A part of the pre-filled syringe, the needle cover, contains latex. Because latex may cause severe allergic reactions, talk to your doctor before using Simponi if you or your carer are allergic to latex.

Sorbitol intolerance
This medicine contains 20.5 mg sorbitol (E420) in each pre-filled syringe.

Polysorbate 80
This medicine contains 0.075 mg of polysorbate 80 (E433) in each pre-filled syringe. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Simponi

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

How much Simponi is given
Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis:
- The recommended dose is 50 mg (the content of 1 pre-filled syringe) given once a month, on the same date each month.
- Talk to your doctor before taking your fourth dose. Your doctor will determine if you should continue Simponi treatment.
    - If you weigh more than 100 kg, the dose might be increased to 100 mg (the content of 2 pre-filled syringes) given once a month, on the same date each month.

Polyarticular juvenile idiopathic arthritis:
- For patients weighing at least 40 kg, the recommended dose is 50 mg given once a month, on the same date each month. For patients weighing less than 40 kg, a 45 mg/0.45 mL pre-filled pen is available. Your doctor will tell you the correct dose to use.

- Talk to your doctor before you take the fourth dose. Your doctor will determine if you should continue Simponi treatment.

Adult ulcerative colitis
- The table below shows how you will usually use this medicine.

Initial treatment	A starting dose of 200 mg (the contents of 4 pre-filled syringes) followed by 100 mg (the contents of 2 pre-filled syringes) 2 weeks later.
Maintenance treatment	• In patients weighing less than 80 kg, 50 mg (the contents of 1 pre-filled syringe) 4 weeks after your last treatment, then every 4 weeks thereafter. Your doctor may decide to prescribe 100 mg (the contents of 2 pre-filled syringes), depending on how well Simponi works for you. • In patients weighing 80 kg or more, 100 mg (the contents of 2 pre-filled syringes) 4 weeks after your last treatment, then every 4 weeks thereafter.

Paediatric ulcerative colitis in children 2 years of age and older weighing at least 15 kg:
- The table below shows how you will usually use this medicine.

Initial treatment	• In patients weighing at least 15 kg to less than 40 kg, a starting dose of 100 mg (the contents of 2 pre-filled syringes) followed by 50 mg (the contents of 1 pre-filled syringe) 2 weeks later. • In patients weighing greater than 40 kg, a starting dose of 200 mg (the contents of 4 pre-filled syringes), followed by 100 mg (the contents of 2 pre-filled syringes) 2 weeks later.
Maintenance treatment	• In patients weighing at least 15 kg to less than 40 kg, 50 mg (the contents of 1 pre-filled syringe) 4 weeks after your last treatment, then every 4 weeks thereafter. • In patients weighing at least 40 kg to less than 80 kg, 100 mg (the contents of 2 pre-filled syringes) 4 weeks after your last treatment, then every 4 weeks thereafter. • In patients weighing 80 kg or more, 100 mg (the contents of 2 pre-filled syringes) 4 weeks after your last treatment, then every 4 weeks thereafter.

Your doctor will tell you the correct dose to use.

How Simponi is given
- Simponi is given by injection under the skin (subcutaneously).
- At the start, your doctor or nurse may inject Simponi. However, you and your doctor may decide that you may inject Simponi yourself. In this case you will get training on how to inject Simponi yourself.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed “Instructions for Use” at the end of this leaflet.

If you use more Simponi than you should
If you have used or been given too much Simponi (either by injecting too much on a single occasion, or by using it too often), talk to your doctor or pharmacist straight away. Always take the outer carton and this leaflet with you, even if it is empty.

If you forget to use Simponi
If you forget to use Simponi on your planned date, inject the forgotten dose as soon as you remember.

Do not use a double dose to make up for a forgotten dose.

When to inject your next dose:
- If you are less than 2 weeks late, inject the forgotten dose as soon as you remember and stay on your original schedule.
- If you are more than 2 weeks late, inject the forgotten dose as soon as you remember and talk to your doctor or pharmacist to ask when you need to take the next dose.

If you are not sure what to do, talk to your doctor or pharmacist.

If you stop using Simponi
If you are considering stopping Simponi, talk to your doctor or pharmacist first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some patients may experience serious side effects and may require treatment. The risk of certain side effects is greater with the 100 mg dose compared with the 50 mg dose. Side effects may appear up to several months after the last injection.

Tell your doctor straight away if you notice any of the following serious side effects of Simponi which include:
- **allergic reactions which may be serious, or rarely, life-threatening (rare).** Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions occurred after the first administration of Simponi.
- **serious infections (including TB, bacterial infections including serious blood infections and pneumonia, severe fungal infections and other opportunistic infections) (common).** Symptoms of an infection can include fever, tiredness, (persistent) cough, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.
- **reactivation of hepatitis B virus if you are a carrier or have had hepatitis B before (rare).** Symptoms can include yellowing of the skin and eyes, dark brown-coloured urine, right-sided abdominal pain, fever, feeling sick, being sick, and feeling very tired.
- **nervous system disease such as multiple sclerosis (rare).** Symptoms of nervous system disease can include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.
- **cancer of the lymph nodes (lymphoma) (rare).** Symptoms of lymphoma can include swelling of the lymph nodes, weight loss, or fever.
- **heart failure (rare).** Symptoms of heart failure can include shortness of breath or swelling of your feet.
- **signs of immune system disorders called:**
  - **lupus (rare).** Symptoms can include joint pain or a rash on cheeks or arms that is sensitive to the sun.
  - **sarcoidosis (rare).** Symptoms can include a persistent cough, being short of breath, chest pain, fever, swelling of your lymph nodes, weight loss, skin rashes, and blurred vision.
- **swelling of small blood vessels (vasculitis) (rare).** Symptoms can include fever, headache, weight loss, night sweats, rash, and nerve problems such as numbness and tingling.
- **skin cancer (uncommon).** Symptoms of skin cancer can include changes in the appearance of your skin or growths on your skin.
- **blood disease (common).** Symptoms of blood disease can include a fever that does not go away, bruising or bleeding very easily or looking very pale.
- **blood cancer (leukaemia) (rare)**. Symptoms of leukaemia can include fever, feeling tired, frequent infections, easy bruising, and night sweats.

Tell your doctor straight away if you notice any of the above symptoms.

The following additional side effects have been observed with Simponi:
Very common side effects (may affect more than 1 in 10 people):
- Upper respiratory tract infections, sore throat or hoarseness, runny nose

Common side effects (may affect up to 1 in 10 people):
- Abnormal liver tests (increased liver enzymes) found during blood tests done by your doctor
- Feeling dizzy
- Headache
- Feeling numb or having a tingling feeling
- Superficial fungal infections
- Abscess
- Bacterial infections (such as cellulitis)
- Low red blood cell counts
- Low white blood cell counts
- Positive blood lupus test
- Allergic reactions
- Indigestion
- Stomach pain
- Feeling sick (nausea)
- Flu
- Bronchitis
- Sinus infection
- Cold sores
- High blood pressure
- Fever
- Asthma, shortness of breath, wheezing
- Stomach and bowel disorders which include inflammation of the stomach lining and colon which may cause fever
- Pain and ulcers in the mouth
- Injection site reactions (including redness, hardness, pain, bruising, itching, tingling and irritation)
- Hair loss
- Rash and itching of the skin
- Difficulty sleeping
- Depression
- Feeling weak
- Bone fractures
- Chest discomfort

Uncommon side effects (may affect up to 1 in 100 people):
- Kidney infection
- Cancers, including skin cancer and non-cancerous growths or lumps, including skin moles
- Skin blisters
- Severe infection throughout the body (sepsis), sometimes including low blood pressure (septic shock)
- Psoriasis (including on the palms of your hand and/or the soles of your feet and/or in the form of skin blisters)
- Low platelet count
- Combined low platelet, red, and white blood cell count
- Thyroid disorders
- Increase in blood sugar levels
- Increase in blood cholesterol levels

- Balance disorders
- Vision disturbances
- Inflamed eye (conjunctivitis)
- Eye allergy
- Sensation of heart beating irregularly
- Narrowing of the blood vessels in the heart
- Blood clots
- Flushing
- Constipation
- Chronic inflammatory condition of the lungs
- Acid reflux
- Gall stones
- Liver disorders
- Breast disorders
- Menstrual disorders

Rare side effects (may affect up to 1 in 1,000 people):
- Failure of the bone marrow to produce blood cells
- Severely decreased number of white blood cells
- Infection of the joints or the tissue around them
- Impaired healing
- Inflammation of blood vessels in internal organs
- Leukaemia
- Melanoma (a type of skin cancer)
- Merkel cell carcinoma (a type of skin cancer)
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes)
- Scaly, peeling skin
- Immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- Pain and discolouration in the fingers or toes
- Taste disturbances
- Bladder disorders
- Kidney disorders
- Inflammation of the blood vessels in your skin which results in rash

Side effects of which the frequency is not known:
- A rare blood cancer affecting mostly young people (hepatosplenic T-cell lymphoma)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Simponi

- 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 label and 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.
- Keep the pre-filled syringe in the outer carton in order to protect it from light.
- This medicine can also be stored out of the refrigerator at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not beyond the original expiry date printed on the carton. Write the new expiry date on the carton including day/month/year (no more than 30 days after the medicine is removed from the refrigerator). Do not return this medicine to refrigerator if it has reached room temperature. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not use this medicine if you notice that the liquid is not a clear to light yellow colour, cloudy, or contains foreign particles.
- Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Simponi contains
The active substance is golimumab. One 0.5 mL pre-filled syringe contains 50 mg of golimumab.
The other ingredients are sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433) and water for injections. For more information on sorbitol (E420) and polysorbate 80 (E433), see Section 2.

What Simponi looks like and contents of the pack
Simponi is supplied as solution for injection in a single-use pre-filled syringe Simponi is available in packs containing 1 pre-filled syringe and multipacks containing 3 (3 packs of 1) pre-filled syringes. Not all pack sizes may be marketed.

The solution is clear to slightly opalescent (having a pearl-like shine), colourless to light yellow and may contain a few small translucent or white particles of protein. Do not use Simponi if the solution is discoloured, cloudy or you can see foreign particles in it.

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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

If you would like to self inject Simponi, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your doctor, nurse or pharmacist to schedule a training session.

In these instructions:
1. Preparing for use of the pre-filled syringe
2. Choosing and preparing the injection site
3. Injecting the medicine
4. After the injection

The diagram below (see figure 1) shows what the pre-filled syringe looks like.

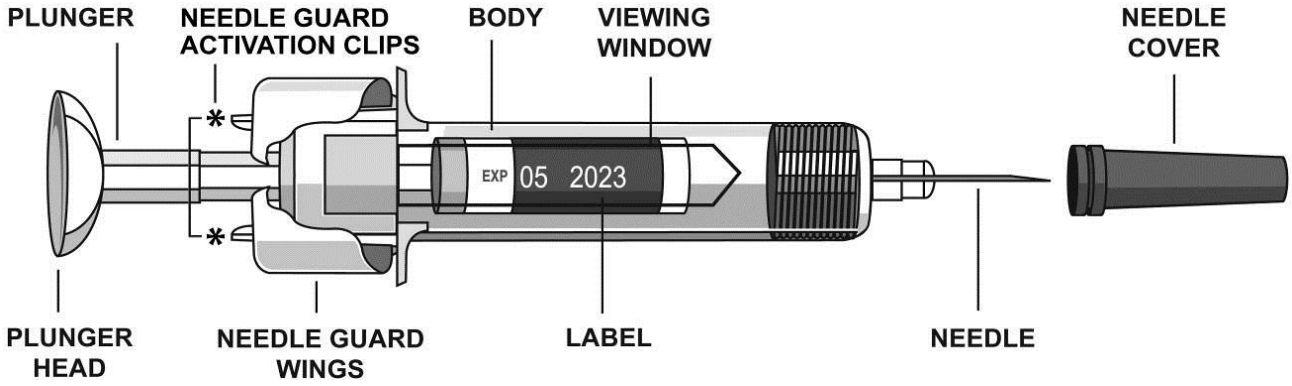


Figure 1

1. Preparing for use of the pre-filled syringe

Hold the pre-filled syringe by the body of the pre-filled syringe
- Do not hold by the plunger head, plunger, needle guard wings, or needle cover.
- Do not pull back on the plunger at any time.
- Do not shake the pre-filled syringe at any time.
- Do not remove the needle cover from the pre-filled syringe until instructed to do so.
- Do not touch the needle guard activation clips (as indicated by asterisks * in figure 1) to prevent prematurely covering the needle with the needle guard.

Check the number of pre-filled syringes
Check the pre-filled syringes to make sure
- the number of pre-filled syringes and strength is correct
  - If your dose is 50 mg, you will get one 50 mg pre-filled syringe
  - If your dose is 100 mg, you will get two 50 mg pre-filled syringes and you will need to give yourself two injections. Choose two different sites for these injections (e.g. one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other.
  - If your dose is 200 mg, you will get four 50 mg pre-filled syringes and you will need to give yourself four injections. Choose different sites for these injections and give the injections one right after the other.

Check expiry date (see figure 2)
- Check the expiry date printed or written on the carton.
- Check the expiry date (as indicated by "EXP") on the label by looking through the viewing window located within the body of the pre-filled syringe.
- If you cannot see the expiry date through the viewing window, hold the pre-filled syringe by its body and rotate the needle cover to line up the expiry date to the viewing window.

Do not use the pre-filled syringe if the expiry date has passed. The printed expiry date refers to the last day of the month. Please contact your doctor or pharmacist for assistance.

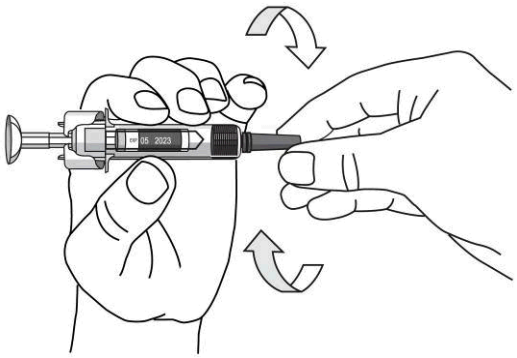


Figure 2

Wait 30 minutes to allow pre-filled syringe to reach room temperature

- To ensure proper injection, allow the pre-filled syringe to sit at room temperature outside the box for 30 minutes, out of the reach of children.

Do not warm the pre-filled syringe in any other way (for example, do not warm it in a microwave or in hot water).
Do not remove the pre-filled syringe's needle cover while allowing it to reach room temperature.

Get the rest of your equipment ready

While you are waiting you can get the rest of your equipment ready, including an alcohol swab, a cotton ball or gauze and a sharps container.

Check the liquid in the pre-filled syringe

- Hold the pre-filled syringe by its body with the covered needle pointing downward.
- Look at the liquid through the viewing window of the pre-filled syringe and make sure that it is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow. The solution can be used if it contains a few small translucent or white particles of protein.
- If you cannot see the liquid through the viewing window, hold the pre-filled syringe by its body and rotate the needle cover to line up the liquid to the viewing window (see figure 2).

Do not use the pre-filled syringe if the liquid is the wrong colour, cloudy, or contains larger particles. If this happens, talk to your doctor or pharmacist.

2. Choosing and preparing the injection site (see figure 3)

- You usually inject the medicine into the front of the middle thighs.
- You can also use the lower stomach (abdomen) below the belly button, except for approximately the 5 cm area directly underneath the belly button.
- Do not inject into areas where the skin is tender, bruised, red, scaly, hard or has scars or stretch marks.
- If multiple injections are required for a single administration, the injections should be administered at different sites on the body.

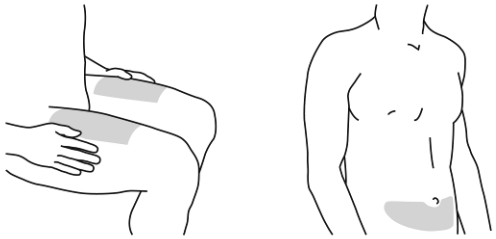


Figure 3

Injection site selection for caregivers (see figure 4)
- If a caregiver is giving you the injection, they can also use the outer area of the upper arms.
- Again, all sites mentioned can be used regardless of your body type or size.

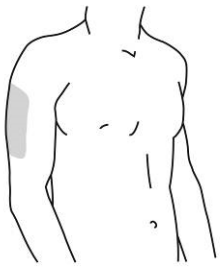


Figure 4

Preparing injection site
- Wash your hands thoroughly with soap and warm water.
- Wipe the injection site with an alcohol swab.
- Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Do not touch this area again before giving the injection.

3. Injecting the medicine

The needle cover should not be removed until you are ready to inject the medicine. The medicine should be injected within 5 minutes after the needle cover has been removed.

Do not touch the plunger during needle cover removal.

Remove the needle cover (see figure 5)
- When you are ready to inject, hold the body of the pre-filled syringe with one hand.
- Pull the needle cover straight off and throw it away after your injection. Do not touch the plunger while you do this.
- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed.
- Inject the dose promptly after removing the needle cover.

Do not touch the needle or allow it to touch any surface.
Do not use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist.

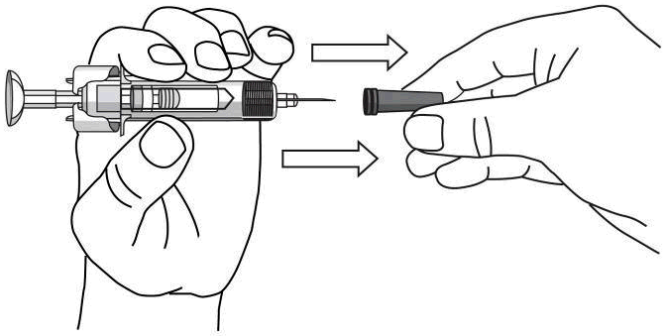


Figure 5

Position the pre-filled syringe to inject

- Hold the body of the pre-filled syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the area of skin that you previously cleaned. Hold firmly.

Do not pull back on the plunger at any time.

Inject the medicine

- Place the needle at approximately a 45-degree angle to the pinched skin. In a single and swift motion, insert the needle through the skin as far as it will go (see figure 6).

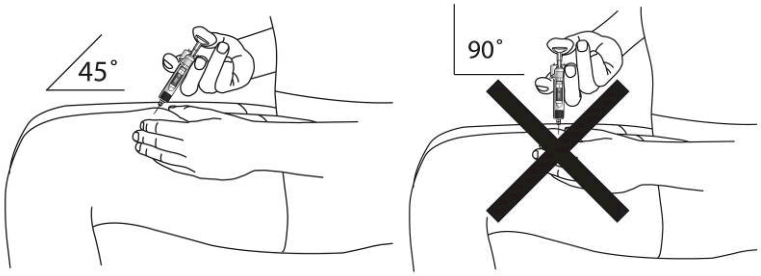


Figure 6

- Inject all of the medicine by pushing in the plunger until the plunger head is completely between the needle guard wings (see figure 7).

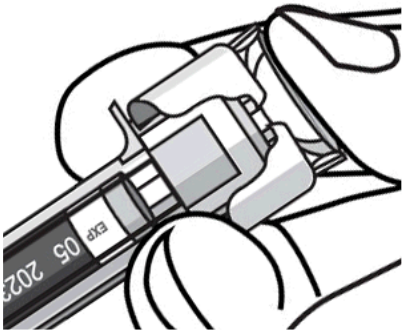


Figure 7

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see figure 8).

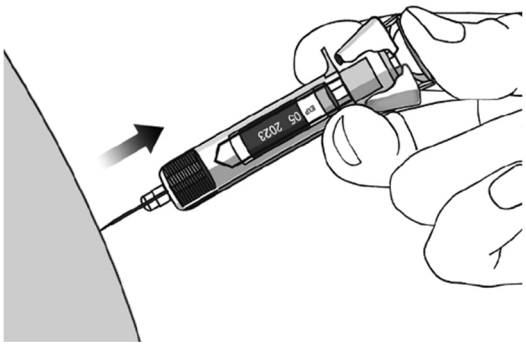


Figure 8

- Slowly take your thumb off the plunger head to allow the empty pre-filled syringe to move up until the entire needle is covered by the needle guard, as shown by the figure 9:

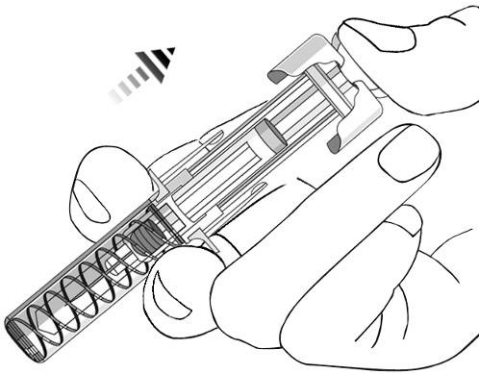


Figure 9

4. After the injection

Use a cotton ball or gauze

- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds.
- You may cover the injection site with a small adhesive bandage, if necessary.

Do not rub your skin.

Throw the pre-filled syringe away (see figure 10)

- Place your pre-filled syringe in a sharps container straight away. Make sure you dispose of the bin as instructed by your doctor or nurse.

Do not attempt to recap the needle.
Do not ever re-use a pre-filled syringe, for your safety and health and for the safety of others.

If you feel that something has gone wrong with the injection or if you are not sure, talk to your doctor or pharmacist.

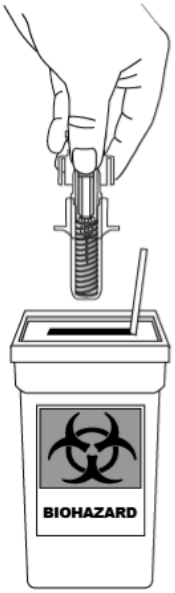


Figure 10

Package Leaflet: Information for the user

Simponi 100 mg solution for injection in pre-filled pen
golimumab

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.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

Your doctor will also give you a Patient Card, which contains important safety information you need to be aware of before and during your treatment with Simponi.

What is in this leaflet

1. What Simponi is and what it is used for
2. What you need to know before you use Simponi
3. How to use Simponi
4. Possible side effects
5. How to store Simponi
6. Contents of the pack and other information

1. What Simponi is and what it is used for

Simponi contains the active substance called golimumab.

Simponi belongs to a group of medicines called 'TNF blockers'. It is used **in adults** for the treatment of the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis
- Ulcerative colitis

Simponi works by blocking the action of a protein called 'tumour necrosis factor alpha' (TNF-α). This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body.

Rheumatoid arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi which you will take in combination with another medicine called methotrexate to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis, an inflammatory disease of the skin. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.

- Improve your physical function.

Ankylosing spondylitis and non-radiographic axial spondyloarthritis
Ankylosing spondylitis and non-radiographic axial spondyloarthritis are inflammatory diseases of the spine. If you have ankylosing spondylitis or non-radiographic axial spondyloarthritis, you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simponi to treat your disease.

2. What you need to know before you use Simponi

Do not use Simponi
- If you are allergic (hypersensitive) to golimumab or any of the other ingredients of this medicine (listed in Section 6).
- If you have tuberculosis (TB) or any other severe infection.
- If you have moderate or severe heart failure.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Simponi.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Simponi.

Infections
Tell your doctor straight away if you already have or get any symptoms of infection, during or after your treatment with Simponi. Symptoms of infection include fever, cough, shortness of breath, flu-like symptoms, diarrhoea, wounds, dental problems or a burning feeling when urinating.
- You may get infections more easily while using Simponi.
- Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

Tuberculosis (TB)
Tell your doctor straight away if symptoms of TB appear during or after your treatment. Symptoms of TB include persistent cough, weight loss, tiredness, fever or night sweats.
- Cases of TB have been reported in patients treated with Simponi, in rare occasions even in patients who have been treated with medicines for TB. Your doctor will test you to see if you have TB. Your doctor will record these tests on your Patient Card.
- It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had or has TB.
- If your doctor feels that you are at risk of TB, you may be treated with medicines for TB before you begin using Simponi.

Hepatitis B virus (HBV)
- Tell your doctor if you are a carrier or if you have or have had HBV before you are given Simponi.
- Tell your doctor if you think you might be at risk of contracting HBV
- Your doctor should test you for HBV
- Treatment with TNF blockers such as Simponi may result in reactivation of HBV in patients who carry this virus, which can be life-threatening in some cases.

Invasive fungal infections
If you have lived in or travelled to an area where infections caused by specific type of fungi that can affect the lungs or other parts of the body (called histoplasmosis, coccidioidomycosis, or blastomycosis), are common, tell your doctor straight away. Ask your doctor if you don't know if these fungal infections are common in the area in which you have lived or travelled.

Cancer and lymphoma
Tell your doctor if you have ever been diagnosed with lymphoma (a type of blood cancer) or any other cancer before you use Simponi.
- If you use Simponi or other TNF blockers, your risk for developing lymphoma or another cancer may increase.
- Patients with severe rheumatoid arthritis and other inflammatory diseases, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
- There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death.
- On rare occasions, a specific and severe type of lymphoma called hepatosplenic T-cell lymphoma has been observed in patients taking other TNF-blockers. Most of these patients were adolescent or young adult males. This type of cancer has usually resulted in death. Almost all of these patients had also received medicines known as azathioprine or 6-mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Simponi.
- Patients with severe persistent asthma, chronic obstructive pulmonary disease (COPD), or are heavy smokers may be at increased risk for cancer with Simponi treatment. If you have severe persistent asthma, COPD or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.
- Some patients treated with golimumab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Heart failure
Tell your doctor straight away if you get new or worsening symptoms of heart failure. Symptoms of heart failure include shortness of breath or swelling of your feet.
- New and worsening congestive heart failure has been reported with TNF blockers, including Simponi. Some of these patients died.
- If you have mild heart failure and you are being treated with Simponi, you must be closely monitored by your doctor.

Nervous system disease
Tell your doctor straight away if you have ever been diagnosed with or develop symptoms of a demyelinating disease such as multiple sclerosis. Symptoms may include changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body. Your doctor will decide if you should receive Simponi.

Operations or dental procedures
- Talk to your doctor if you are going to have any operations or dental procedures.
- Tell your surgeon or dentist performing the procedure that you are having treatment with Simponi by showing them your Patient Card.

Autoimmune disease
Tell your doctor if you develop symptoms of a disease called lupus. Symptoms include persistent rash, fever, joint pain and tiredness.
- On rare occasions, people treated with TNF blockers have developed lupus.

Blood disease
In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Vaccinations
Talk to your doctor if you have had, or are due to have a vaccine.
- You should not receive certain (live) vaccines while using Simponi.
- Certain vaccinations may cause infections. If you received Simponi while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Simponi use so they can decide when your baby should receive any vaccine.

Therapeutic infectious agents
Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Allergic reactions
Tell your doctor straight away if you develop symptoms of an allergic reaction after your treatment with Simponi. Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles.
- Some of these reactions may be serious or, rarely, life-threatening.
- Some of these reactions occurred after the first administration of Simponi.

Children and adolescents
Simponi 100 mg pre-filled pen is not recommended for children and adolescents (younger than 18 years).

Other medicines and Simponi
- Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including any other medicines to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis.
- You should not take Simponi with medicines containing the active substance anakinra or abatacept. These medicines are used for the treatment of rheumatic diseases.
- Tell your doctor or pharmacist if you are taking any other medicines that affect your immune system.
- You should not receive certain (live) vaccines while using Simponi.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Pregnancy and breast-feeding
Talk to your doctor before using Simponi if:
- You are pregnant or are planning to become pregnant while using Simponi. There is limited information about the effects of this medicine in pregnant women. If you are being treated with Simponi, you must avoid becoming pregnant by using adequate contraception during your treatment and for at least 6 months after the last Simponi injection. Simponi should only be used during pregnancy if it is clearly necessary for you.
- Before starting breast-feeding, your last treatment with Simponi must be at least 6 months ago. You must stop breast-feeding if you are to be given Simponi.

- If you received Simponi during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Simponi use before the baby receives any vaccine (for more information see section on vaccination).

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Simponi has minor influence on your ability to drive and use tools or machines. Dizziness may however occur after you take Simponi. If this happens, do not drive or use any tools or machines.

Simponi contains latex, sorbitol and polysorbate
Latex sensitivity
A part of the pre-filled pen, the needle cover, contains latex. Because latex may cause severe allergic reactions, talk to your doctor before using Simponi if you or your carer are allergic to latex.

Sorbitol intolerance
This medicine contains 41 mg sorbitol (E420) in each pre-filled pen.

Polysorbate 80
This medicine contains 0.15 mg of polysorbate 80 (E433) in each pre-filled pen. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Simponi

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

How much Simponi is given
Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis:
- The recommended dose is 50 mg given once a month, on the same date each month.
- Talk to your doctor before taking your fourth dose. Your doctor will determine if you should continue Simponi treatment.
    - If you weigh more than 100 kg, the dose might be increased to 100 mg (the content of 1 pre-filled pen) given once a month, on the same date each month.

Ulcerative colitis
- The table below shows how you will usually use this medicine.

Initial treatment	A starting dose of 200 mg (the contents of 2 pre-filled pens) followed by 100 mg (the contents of 1 pre-filled pen) 2 weeks later.
Maintenance treatment	• In patients weighing less than 80 kg, 50 mg (the 50 mg pre-filled pen or pre-filled syringe must be used to administer this dose) 4 weeks after your last treatment, then every 4 weeks thereafter. Your doctor may decide to prescribe 100 mg (the contents of 1 pre-filled pen), depending on how well Simponi works for you. • In patients weighing 80 kg or more, 100 mg (the contents of 1 pre-filled pen) 4 weeks after your last treatment, then every 4 weeks thereafter.

How Simponi is given
- Simponi is given by injection under the skin (subcutaneously).

- At the start, your doctor or nurse may inject Simponi. However, you and your doctor may decide that you may inject Simponi yourself. In this case you will get training on how to inject Simponi yourself.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed “Instructions for Use” at the end of this leaflet.

If you use more Simponi than you should
If you have used or been given too much Simponi (either by injecting too much on a single occasion, or by using it too often), talk to your doctor or pharmacist straight away. Always take the outer carton and this leaflet with you, even if it is empty.

If you forget to use Simponi
If you forget to use Simponi on your planned date, inject the forgotten dose as soon as you remember.

Do not use a double dose to make up for a forgotten dose.

When to inject your next dose:
- If you are less than 2 weeks late, inject the forgotten dose as soon as you remember and stay on your original schedule.
- If you are more than 2 weeks late, inject the forgotten dose as soon as you remember and talk to your doctor or pharmacist to ask when you need to take the next dose.

If you are not sure what to do, talk to your doctor or pharmacist.

If you stop using Simponi
If you are considering stopping Simponi, talk to your doctor or pharmacist first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some patients may experience serious side effects and may require treatment. The risk of certain side effects is greater with the 100 mg dose compared with the 50 mg dose. Side effects may appear up to several months after the last injection.

Tell your doctor straight away if you notice any of the following serious side effects of Simponi which include:
- **allergic reactions which may be serious, or rarely, life-threatening (rare).** Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions occurred after the first administration of Simponi.
- **serious infections (including TB, bacterial infections including serious blood infections and pneumonia, severe fungal infections and other opportunistic infections) (common).** Symptoms of an infection can include fever, tiredness, (persistent) cough, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.
- **reactivation of hepatitis B virus if you are a carrier or have had hepatitis B before (rare).** Symptoms can include yellowing of the skin and eyes, dark brown-coloured urine, right-sided abdominal pain, fever, feeling sick, being sick, and feeling very tired.
- **nervous system disease such as multiple sclerosis (rare).** Symptoms of nervous system disease can include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.
- **cancer of the lymph nodes (lymphoma) (rare).** Symptoms of lymphoma can include swelling of the lymph nodes, weight loss, or fever.

- **heart failure (rare).** Symptoms of heart failure can include shortness of breath or swelling of your feet.
- **signs of immune system disorders called:**
  - **lupus (rare).** Symptoms can include joint pain or a rash on cheeks or arms that is sensitive to the sun.
  - **sarcoidosis (rare).** Symptoms can include a persistent cough, being short of breath, chest pain, fever, swelling of your lymph nodes, weight loss, skin rashes, and blurred vision.
- **swelling of small blood vessels (vasculitis) (rare).** Symptoms can include fever, headache, weight loss, night sweats, rash, and nerve problems such as numbness and tingling.
- **skin cancer (uncommon).** Symptoms of skin cancer can include changes in the appearance of your skin or growths on your skin.
- **blood disease (common).** Symptoms of blood disease can include a fever that does not go away, bruising or bleeding very easily or looking very pale.
- **blood cancer (leukaemia) (rare).** Symptoms of leukaemia can include fever, feeling tired, frequent infections, easy bruising, and night sweats.

Tell your doctor straight away if you notice any of the above symptoms.

The following additional side effects have been observed with Simponi:

Very common side effects (may affect more than 1 in 10 people):

- Upper respiratory tract infections, sore throat or hoarseness, runny nose

Common side effects (may affect up to 1 in 10 people):

- Abnormal liver tests (increased liver enzymes) found during blood tests done by your doctor
- Feeling dizzy
- Headache
- Feeling numb or having a tingling feeling
- Superficial fungal infections
- Abscess
- Bacterial infections (such as cellulitis)
- Low red blood cell counts
- Low white blood cell counts
- Positive blood lupus test
- Allergic reactions
- Indigestion
- Stomach pain
- Feeling sick (nausea)
- Flu
- Bronchitis
- Sinus infection
- Cold sores
- High blood pressure
- Fever
- Asthma, shortness of breath, wheezing
- Stomach and bowel disorders which include inflammation of the stomach lining and colon which may cause fever
- Pain and ulcers in the mouth
- Injection site reactions (including redness, hardness, pain, bruising, itching, tingling and irritation)
- Hair loss
- Rash and itching of the skin
- Difficulty sleeping
- Depression
- Feeling weak
- Bone fractures
- Chest discomfort

Uncommon side effects (may affect up to 1 in 100 people):

- Kidney infection
- Cancers, including skin cancer and non-cancerous growths or lumps, including skin moles
- Skin blisters
- Severe infection throughout the body (sepsis), sometimes including low blood pressure (septic shock)
- Psoriasis (including on the palms of your hand and/or the soles of your feet and/or in the form of skin blisters)
- Low platelet count
- Combined low platelet, red, and white blood cell count
- Thyroid disorders
- Increase in blood sugar levels
- Increase in blood cholesterol levels
- Balance disorders
- Vision disturbances
- Inflamed eye (conjunctivitis)
- Eye allergy
- Sensation of heart beating irregularly
- Narrowing of the blood vessels in the heart
- Blood clots
- Flushing
- Constipation
- Chronic inflammatory condition of the lungs
- Acid reflux
- Gall stones
- Liver disorders
- Breast disorders
- Menstrual disorders

Rare side effects (may affect up to 1 in 1,000 people):

- Failure of the bone marrow to produce blood cells
- Severely decreased number of white blood cells
- Infection of the joints or the tissue around them
- Impaired healing
- Inflammation of blood vessels in internal organs
- Leukaemia
- Melanoma (a type of skin cancer)
- Merkel cell carcinoma (a type of skin cancer)
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes)
- Scaly, peeling skin
- Immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- Pain and discolouration in the fingers or toes
- Taste disturbances
- Bladder disorders
- Kidney disorders
- Inflammation of the blood vessels in your skin which results in rash

Side effects of which the frequency is not known:

- A rare blood cancer affecting mostly young people (hepatosplenic T-cell lymphoma)
- Kaposi’s sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi’s sarcoma most commonly appears as purple lesions on the skin

- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Simponi

- 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 label and 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.
- Keep the pre-filled pen in the outer carton in order to protect it from light.
- This medicine can also be stored out of the refrigerator at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not beyond the original expiry date printed on the carton. Write the new expiry date on the carton including day/month/year (no more than 30 days after the medicine is removed from the refrigerator). Do not return this medicine to refrigerator if it has reached room temperature. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not use this medicine if you notice that the liquid is not a clear to light yellow colour, cloudy, or contains foreign particles.
- Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Simponi contains
The active substance is golimumab. One 1 mL pre-filled pen contains 100 mg of golimumab.

The other ingredients are sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433) and water for injections. For more information on sorbitol (E420) and polysorbate 80 (E433), see Section 2.

What Simponi looks like and contents of the pack
Simponi is supplied as solution for injection in a single-use pre-filled pen. Simponi is available in packs containing 1 pre-filled pen and multipacks containing 3 (3 packs of 1) pre-filled pens. Not all pack sizes may be marketed.

The solution is clear to slightly opalescent (having a pearl-like shine), colourless to light yellow and may contain a few small translucent or white particles of protein. Do not use Simponi if the solution is discoloured, cloudy or you can see foreign particles in it.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

INSTRUCTIONS FOR USE

If you would like to self inject Simponi, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your doctor, nurse or pharmacist to schedule a training session.

In these instructions:
1. Preparing for use of the pre-filled pen
2. Choosing and preparing the injection site
3. Injecting the medicine
4. After the injection

The diagram below (see figure 1) shows what the "SmartJect" pre-filled pen looks like.

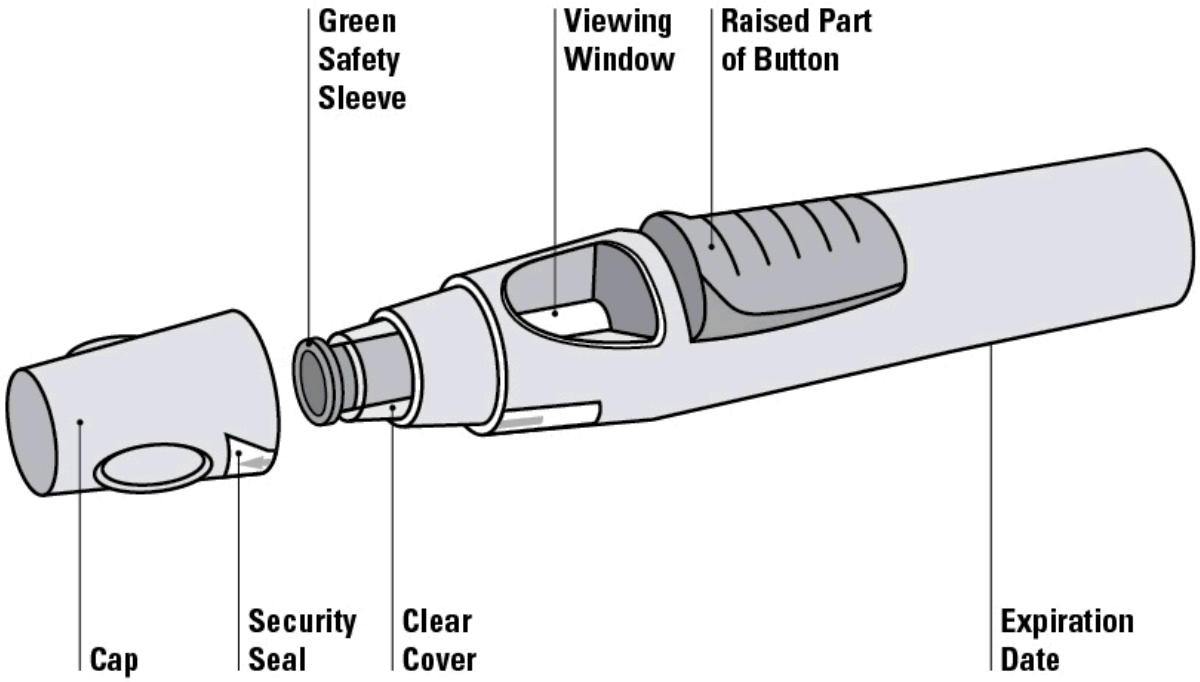


Figure 1

1. Preparing for use of the pre-filled pen

- Do not shake the pre-filled pen at any time.
- Do not remove the cap from the pre-filled pen until immediately before the injection.
- Do not put the cap of the pre-filled pen back on if removed to avoid bending the needle.

Check the number of pre-filled pens
Check the pre-filled pens to make sure
- the number of pre-filled pens and strength is correct
  - If your dose is 100 mg, you will get one 100 mg pre-filled pen
  - If your dose is 200 mg, you will get two 100 mg pre-filled pens and you will need to give yourself two injections. Choose different sites for these injections and give the injections one right after the other.

Check expiry date
- Check the expiry date printed or written on the carton.
- Check the expiry date (as indicated as "EXP") on the pre-filled pen.
- Do not use the pre-filled pen if the expiry date has passed. The printed expiry date refers to the last day of the month. Please contact your doctor or pharmacist for assistance.

Check security seal
- Check the security seal around the cap of the pre-filled pen.
- Do not use the pre-filled pen if the seal is broken. Please contact your doctor or pharmacist.

Wait 30 minutes to allow pre-filled pen to reach room temperature
- To ensure proper injection, allow the pre-filled pen to sit at room temperature outside the box for 30 minutes out of the reach of children.
- Do not warm the pre-filled pen in any other way (for example, do not warm it in a microwave or in hot water).
- Do not remove the pre-filled pen's cap while allowing it to reach room temperature.

Get the rest of your equipment ready
- While you are waiting you can get the rest of your equipment ready, including an alcohol swab, a cotton ball or gauze and a sharps container.

Check the liquid in the pre-filled pen
- Look through the viewing window to make sure that the liquid in the pre-filled pen is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow. The solution can be used if it contains a few small translucent or white particles of protein.
- You will also notice an air bubble, which is normal.
- Do not use the pre-filled pen if the liquid is the wrong colour, cloudy, or contains larger particles. If this happens, talk to your doctor or pharmacist.

2. Choosing and preparing the injection site (see figure 2)

- You can inject the medicine into the front of the middle thighs.
- You can use the stomach (abdomen) below the belly button, except for approximately the 5 cm area directly underneath the belly button.
- Do not inject into areas where the skin is tender, bruised, red, scaly, hard or has scars or stretch marks.
- If multiple injections are required for a single administration, the injections should be administered at different injection sites.

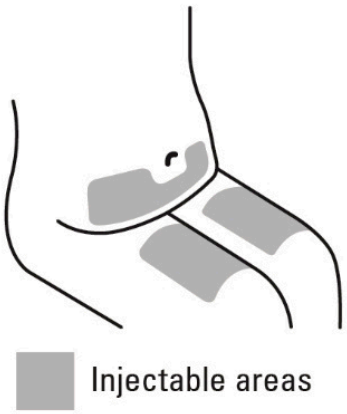


Figure 2

⚠ **DO NOT** inject into the arm to avoid failure of the pre-filled pen and/or unintentional injury.

Wash hands and clean injection site
- Wash your hands thoroughly with soap and warm water.
- Wipe the injection site with an alcohol swab.
- Allow the skin to dry before injecting. Do not fan or blow on the clean area.
- Do not touch this area again before giving the injection.

3. Injecting the medicine

- The cap should not be removed until you are ready to inject the medicine.
- The medicine should be injected within 5 minutes after the cap has been removed.

Remove the cap (figure 3)
- When you are ready to inject, twist the cap slightly to break the security seal.
- Pull the cap off and throw it away after your injection.

- Do not put the cap back on because it may damage the needle inside the pre-filled pen.
- Do not use the pre-filled pen if it is dropped without the cap in place. If this happens please contact your doctor or pharmacist.

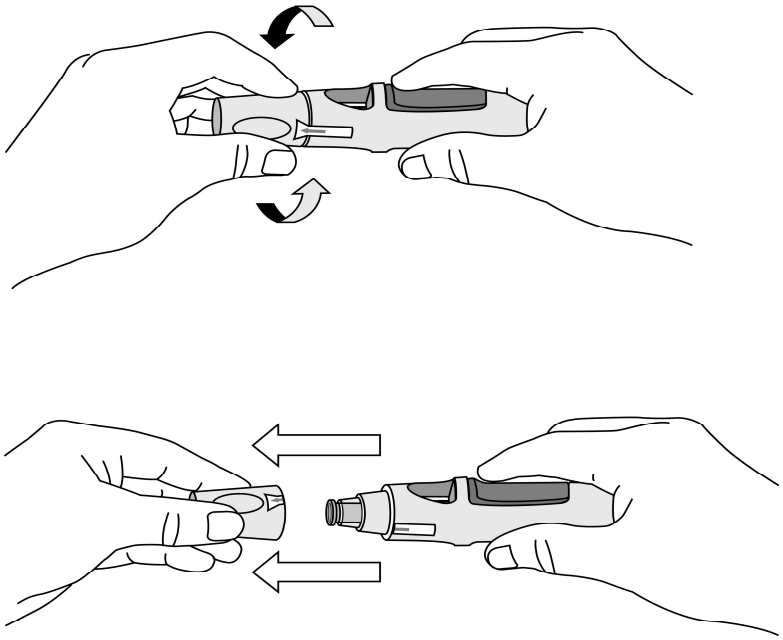


Figure 3

Push the pre-filled pen against the skin (see figures 4 and 5) without pinching the skin.

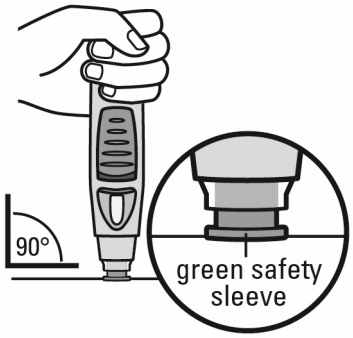


Figure 4

- Hold the pre-filled pen comfortably with one hand **above the blue button**.
- Make sure the green safety sleeve is stable and is as flat as possible against your skin. If the pre-filled pen is not stable during the injection, you risk bending the needle.
- DO NOT pinch the skin to avoid unintentional needlestick injury.
- DO NOT touch or press the blue button while positioning the pre-filled pen onto your skin.

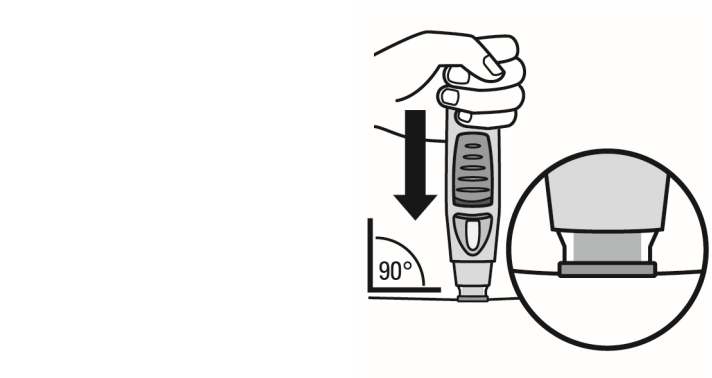


Figure 5

- Push the open end of the pre-filled pen against the skin at a 90-degree angle. Apply enough pressure to slide the green safety sleeve up and to maintain it inside the clear cover. Only the wider portion of the green safety sleeve remains outside of the clear cover.
- DO NOT press the blue button until after the safety sleeve slides into the clear cover. Pushing the blue button before the safety sleeve is depressed can lead to pen failure.
- Inject without pinching the skin.

Press button to inject (see figures 6 and 7)

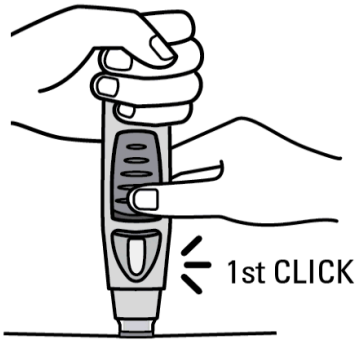


Figure 6

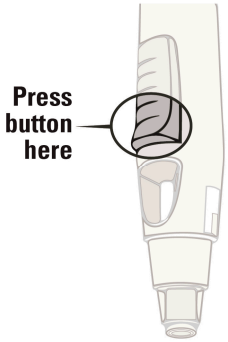


Figure 7

- Continue to push the pre-filled pen against your skin. **Use your other hand** to press the **raised part of the blue button** to start your injection. Do not press the button unless the pre-filled pen is **pressed against your skin** and the safety sleeve slides into the clear cover.
- Once the button is pressed, it will remain pressed in so you do not need to keep pressure on it.
- If the button seems hard to depress, don't press the button harder. Let go of the button, lift the pre-filled pen and start again. Ensure no pressure is on the button until the green safety sleeve is fully depressed against the skin, then press the raised part of the button.
- **You will hear a loud 'click' sound – don't be alarmed.** The first 'click' means that the needle has been inserted and the injection has started. You may or may not feel a needle prick at this time.

Do not lift the pre-filled pen away from your skin. If you pull the pre-filled pen away from your skin, you may not get your full dose of medicine.

Continue to hold until the second 'click' (see figure 8), it usually takes about 3 to 6 seconds, but may take up to 15 seconds for you to hear the second 'click' sound.

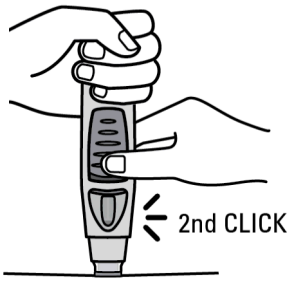


Figure 8

- **Continue to hold the pre-filled pen against your skin until you hear a second 'click' (indicating that the injection has finished and the needle has gone back into the pre-filled pen).**
- Lift the pre-filled pen from the injection site.
- Note: If you do not hear the second 'click', wait 15 seconds from the time you first press the button and then lift the autoinjector from the injection site.

4. After the injection

Use a cotton ball or gauze
- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site for 10 seconds.
- You may cover the injection site with a small adhesive bandage, if necessary.
- Do not rub your skin.

Check the window – a yellow indicator confirms proper administration (see figure 9)
- The yellow indicator is connected to the plunger of the pre-filled pen. If the yellow indicator is not shown in the window, the plunger has not advanced adequately, and the injection has not occurred.
- The yellow indicator will fill about half of the viewing window. This is normal.
- Talk to your doctor or pharmacist if the yellow indicator is not visible in the window or if you suspect that you may not have received a complete dose. Do not administer a second dose without speaking to your doctor.

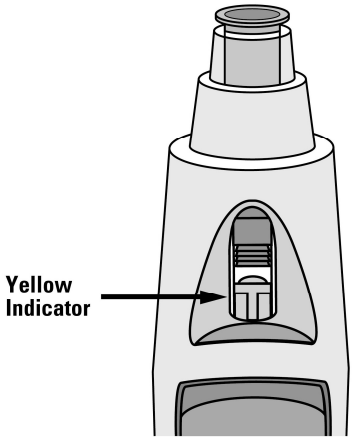


Figure 9

Throw the pre-filled pen away (see figure 10)
- Place your pen in a sharps container straight away. Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.

If you feel that something has gone wrong with the injection or if you are not sure, talk to your doctor or pharmacist.



Figure 10

Package Leaflet: Information for the user

Simponi 100 mg solution for injection in pre-filled syringe
golimumab

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.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

Your doctor will also give you a Patient Card, which contains important safety information you need to be aware of before and during your treatment with Simponi.

What is in this leaflet

1. What Simponi is and what it is used for
2. What you need to know before you use Simponi
3. How to use Simponi
4. Possible side effects
5. How to store Simponi
6. Contents of the pack and other information

1. What Simponi is and what it is used for

Simponi contains the active substance called golimumab.

Simponi belongs to a group of medicines called 'TNF blockers'. It is used **in adults** for the treatment of the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis
- Ulcerative colitis

In children 2 years of age and older and above 15 kg, Simponi is used for the treatment of paediatric ulcerative colitis.

Simponi works by blocking the action of a protein called 'tumour necrosis factor alpha' (TNF-α). This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body.

Rheumatoid arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi which you will take in combination with another medicine called methotrexate to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis, an inflammatory disease of the skin. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Ankylosing spondylitis and non-radiographic axial spondyloarthritis
Ankylosing spondylitis and non-radiographic axial spondyloarthritis are inflammatory diseases of the spine. If you have ankylosing spondylitis or non-radiographic axial spondyloarthritis, you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.

Ulcerative colitis (adult and paediatric)
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Simponi to treat your disease.

2. What you need to know before you use Simponi

Do not use Simponi
- If you are allergic (hypersensitive) to golimumab or any of the other ingredients of this medicine (listed in Section 6).
- If you have tuberculosis (TB) or any other severe infection.
- If you have moderate or severe heart failure.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Simponi.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Simponi.

Infections
Tell your doctor straight away if you already have or get any symptoms of infection, during or after your treatment with Simponi. Symptoms of infection include fever, cough, shortness of breath, flu-like symptoms, diarrhoea, wounds, dental problems or a burning feeling when urinating.
- You may get infections more easily while using Simponi.
- Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

  Tuberculosis (TB)
  Tell your doctor straight away if symptoms of TB appear during or after your treatment. Symptoms of TB include persistent cough, weight loss, tiredness, fever or night sweats.
  - Cases of TB have been reported in patients treated with Simponi, in rare occasions even in patients who have been treated with medicines for TB. Your doctor will test you to see if you have TB. Your doctor will record these tests on your Patient Card.
  - It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had or has TB.
  - If your doctor feels that you are at risk of TB, you may be treated with medicines for TB before you begin using Simponi.

Hepatitis B virus (HBV)

- Tell your doctor if you are a carrier or if you have or have had HBV before you are given Simponi.
- Tell your doctor if you think you might be at risk of contracting HBV
- Your doctor should test you for HBV
- Treatment with TNF blockers such as Simponi may result in reactivation of HBV in patients who carry this virus, which can be life-threatening in some cases.

Invasive fungal infections

If you have lived in or travelled to an area where infections caused by specific type of fungi that can affect the lungs or other parts of the body (called histoplasmosis, coccidioidomycosis, or blastomycosis), are common, tell your doctor straight away. Ask your doctor if you don't know if these fungal infections are common in the area in which you have lived or travelled.

Cancer and lymphoma

Tell your doctor if you have ever been diagnosed with lymphoma (a type of blood cancer) or any other cancer before you use Simponi.

- If you use Simponi or other TNF blockers, your risk for developing lymphoma or another cancer may increase.
- Patients with severe rheumatoid arthritis and other inflammatory diseases, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
- There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death.
- On rare occasions, a specific and severe type of lymphoma called hepatosplenic T-cell lymphoma has been observed in patients taking other TNF-blockers. Most of these patients were adolescent or young adult males. This type of cancer has usually resulted in death. Almost all of these patients had also received medicines known as azathioprine or 6-mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Simponi.
- Patients with severe persistent asthma, chronic obstructive pulmonary disease (COPD), or are heavy smokers may be at increased risk for cancer with Simponi treatment. If you have severe persistent asthma, COPD or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.
- Some patients treated with golimumab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Heart failure

Tell your doctor straight away if you get new or worsening symptoms of heart failure. Symptoms of heart failure include shortness of breath or swelling of your feet.

- New and worsening congestive heart failure has been reported with TNF blockers, including Simponi. Some of these patients died.
- If you have mild heart failure and you are being treated with Simponi, you must be closely monitored by your doctor.

Nervous system disease

Tell your doctor straight away if you have ever been diagnosed with or develop symptoms of a demyelinating disease such as multiple sclerosis. Symptoms may include changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body. Your doctor will decide if you should receive Simponi.

Operations or dental procedures

- Talk to your doctor if you are going to have any operations or dental procedures.
- Tell your surgeon or dentist performing the procedure that you are having treatment with Simponi by showing them your Patient Card.

Autoimmune disease
Tell your doctor if you develop symptoms of a disease called lupus. Symptoms include persistent rash, fever, joint pain and tiredness.
- On rare occasions, people treated with TNF blockers have developed lupus.

Blood disease
In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Vaccinations
Talk to your doctor if you have had, or are due to have a vaccine.
- You should not receive certain (live) vaccines while using Simponi.
- Certain vaccinations may cause infections. If you received Simponi while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Simponi use so they can decide when your baby should receive any vaccine.

Therapeutic infectious agents
Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Allergic reactions
Tell your doctor straight away if you develop symptoms of an allergic reaction after your treatment with Simponi. Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles.
- Some of these reactions may be serious or, rarely, life-threatening.
- Some of these reactions occurred after the first administration of Simponi.

Children
Simponi is not recommended for children less than 2 years of age with paediatric ulcerative colitis because it has not been studied in this group.

Other medicines and Simponi
- Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including any other medicines to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis.
- You should not take Simponi with medicines containing the active substance anakinra or abatacept. These medicines are used for the treatment of rheumatic diseases.
- Tell your doctor or pharmacist if you are taking any other medicines that affect your immune system.
- You should not receive certain (live) vaccines while using Simponi.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Pregnancy and breast-feeding
Talk to your doctor before using Simponi if:
- You are pregnant or are planning to become pregnant while using Simponi. There is limited information about the effects of this medicine in pregnant women. If you are being treated with Simponi, you must avoid becoming pregnant by using adequate contraception during your

treatment and for at least 6 months after the last Simponi injection. Simponi should only be used during pregnancy if it is clearly necessary for you.
- Before starting breast-feeding, your last treatment with Simponi must be at least 6 months ago. You must stop breast-feeding if you are to be given Simponi.
- If you received Simponi during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Simponi use before the baby receives any vaccine (for more information see section on vaccination).

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Simponi has minor influence on your ability to drive and use tools or machines. Dizziness may however occur after you take Simponi. If this happens, do not drive or use any tools or machines.

Simponi contains latex, sorbitol and polysorbate
Latex sensitivity
A part of the pre-filled syringe, the needle cover, contains latex. Because latex may cause severe allergic reactions, talk to your doctor before using Simponi if you or your carer are allergic to latex.

Sorbitol intolerance
This medicine contains 41 mg sorbitol (E420) in each pre-filled syringe.

Polysorbate 80
This medicine contains 0.15 mg of polysorbate 80 (E433) in each pre-filled syringe. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Simponi

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

How much Simponi is given
Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis:
- The recommended dose is 50 mg given once a month, on the same date each month.
- Talk to your doctor before taking your fourth dose. Your doctor will determine if you should continue Simponi treatment.
    - If you weigh more than 100 kg, the dose might be increased to 100 mg (the content of 1 pre-filled syringe) given once a month, on the same date each month.

Adult ulcerative colitis
- The table below shows how you will usually use this medicine.

Initial treatment	A starting dose of 200 mg (the contents of 2 pre-filled syringes) followed by 100 mg (the contents of 1 pre-filled syringe) 2 weeks later.
Maintenance treatment	• In patients weighing less than 80 kg, 50 mg (the 50 mg pre-filled pen or pre-filled syringe must be used to administer this dose) 4 weeks after your last treatment, then every 4 weeks thereafter. Your doctor may decide to prescribe 100 mg (the contents of 1 pre-filled syringe) depending on how well Simponi works for you. • In patients weighing 80 kg or more, 100 mg (the contents of 1 pre-filled syringe) 4 weeks after your last treatment, then every 4 weeks thereafter.

Paediatric ulcerative colitis in children 2 years of age and older weighing at least 15 kg:

- The table below shows how you will usually use this medicine.

Initial treatment	• In patients weighing at least 15 kg to less than 40 kg, a starting dose of 100 mg (the contents of 1 pre-filled syringe) followed by 50 mg (the 50 mg pre-filled syringe must be used to administer this dose) 2 weeks later. • In patients weighing greater than 40 kg, a starting dose of 200 mg (the contents of 2 pre-filled syringes), followed by 100 mg (the contents of 1 pre-filled syringe) 2 weeks later.
Maintenance treatment	• In patients weighing at least 15 kg to less than 40 kg, 50 mg (the 50 mg pre-filled syringe must be used to administer this dose) 4 weeks after your last treatment, then every 4 weeks thereafter. • In patients weighing at least 40 kg to less than 80 kg, 100 mg (the contents of 1 pre-filled syringe) 4 weeks after your last treatment, then every 4 weeks thereafter. • In patients weighing 80 kg or more, 100 mg (the contents of 1 pre-filled syringe) 4 weeks after your last treatment, then every 4 weeks thereafter.

Your doctor will tell you the correct dose to use.

How Simponi is given

- Simponi is given by injection under the skin (subcutaneously).
- At the start, your doctor or nurse may inject Simponi. However, you and your doctor may decide that you may inject Simponi yourself. In this case you will get training on how to inject Simponi yourself.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed “Instructions for Use” at the end of this leaflet.

If you use more Simponi than you should

If you have used or been given too much Simponi (either by injecting too much on a single occasion, or by using it too often), talk to your doctor or pharmacist straight away. Always take the outer carton and this leaflet with you, even if it is empty.

If you forget to use Simponi

If you forget to use Simponi on your planned date, inject the forgotten dose as soon as you remember.

Do not use a double dose to make up for a forgotten dose.

When to inject your next dose:

- If you are less than 2 weeks late, inject the forgotten dose as soon as you remember and stay on your original schedule.
- If you are more than 2 weeks late, inject the forgotten dose as soon as you remember and talk to your doctor or pharmacist to ask when you need to take the next dose.

If you are not sure what to do, talk to your doctor or pharmacist.

If you stop using Simponi

If you are considering stopping Simponi, talk to your doctor or pharmacist first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some patients may experience serious side effects and may require treatment. The risk of certain side effects is greater with the 100 mg dose compared with the 50 mg dose. Side effects may appear up to several months after the last injection.

Tell your doctor straight away if you notice any of the following serious side effects of Simponi which include:

- **allergic reactions which may be serious, or rarely, life-threatening (rare).** Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions occurred after the first administration of Simponi.
- **serious infections (including TB, bacterial infections including serious blood infections and pneumonia, severe fungal infections and other opportunistic infections) (common).** Symptoms of an infection can include fever, tiredness, (persistent) cough, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.
- **reactivation of hepatitis B virus if you are a carrier or have had hepatitis B before (rare).** Symptoms can include yellowing of the skin and eyes, dark brown-coloured urine, right-sided abdominal pain, fever, feeling sick, being sick, and feeling very tired.
- **nervous system disease such as multiple sclerosis (rare).** Symptoms of nervous system disease can include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.
- **cancer of the lymph nodes (lymphoma) (rare).** Symptoms of lymphoma can include swelling of the lymph nodes, weight loss, or fever.
- **heart failure (rare).** Symptoms of heart failure can include shortness of breath or swelling of your feet.
- **signs of immune system disorders called:**
  - **lupus (rare).** Symptoms can include joint pain or a rash on cheeks or arms that is sensitive to the sun.
  - **sarcoidosis (rare).** Symptoms can include a persistent cough, being short of breath, chest pain, fever, swelling of your lymph nodes, weight loss, skin rashes, and blurred vision.
- **swelling of small blood vessels (vasculitis) (rare).** Symptoms can include fever, headache, weight loss, night sweats, rash, and nerve problems such as numbness and tingling.
- **skin cancer (uncommon).** Symptoms of skin cancer can include changes in the appearance of your skin or growths on your skin.
- **blood disease (common).** Symptoms of blood disease can include a fever that does not go away, bruising or bleeding very easily or looking very pale.
- **blood cancer (leukaemia) (rare)**. Symptoms of leukaemia can include fever, feeling tired, frequent infections, easy bruising, and night sweats.

Tell your doctor straight away if you notice any of the above symptoms.

The following additional side effects have been observed with Simponi:

<u>Very common side effects (may affect more than 1 in 10 people):</u>

- Upper respiratory tract infections, sore throat or hoarseness, runny nose

<u>Common side effects (may affect up to 1 in 10 people):</u>

- Abnormal liver tests (increased liver enzymes) found during blood tests done by your doctor
- Feeling dizzy
- Headache
- Feeling numb or having a tingling feeling
- Superficial fungal infections
- Abscess
- Bacterial infections (such as cellulitis)
- Low red blood cell counts

- Low white blood cell counts
- Positive blood lupus test
- Allergic reactions
- Indigestion
- Stomach pain
- Feeling sick (nausea)
- Flu
- Bronchitis
- Sinus infection
- Cold sores
- High blood pressure
- Fever
- Asthma, shortness of breath, wheezing
- Stomach and bowel disorders which include inflammation of the stomach lining and colon which may cause fever
- Pain and ulcers in the mouth
- Injection site reactions (including redness, hardness, pain, bruising, itching, tingling and irritation)
- Hair loss
- Rash and itching of the skin
- Difficulty sleeping
- Depression
- Feeling weak
- Bone fractures
- Chest discomfort

Uncommon side effects (may affect up to 1 in 100 people):

- Kidney infection
- Cancers, including skin cancer and non-cancerous growths or lumps, including skin moles
- Skin blisters
- Severe infection throughout the body (sepsis), sometimes including low blood pressure (septic shock)
- Psoriasis (including on the palms of your hand and/or the soles of your feet and/or in the form of skin blisters)
- Low platelet count
- Combined low platelet, red, and white blood cell count
- Thyroid disorders
- Increase in blood sugar levels
- Increase in blood cholesterol levels
- Balance disorders
- Vision disturbances
- Inflamed eye (conjunctivitis)
- Eye allergy
- Sensation of heart beating irregularly
- Narrowing of the blood vessels in the heart
- Blood clots
- Flushing
- Constipation
- Chronic inflammatory condition of the lungs
- Acid reflux
- Gall stones
- Liver disorders
- Breast disorders
- Menstrual disorders

Rare side effects (may affect up to 1 in 1,000 people):
- Failure of the bone marrow to produce blood cells
- Severely decreased number of white blood cells
- Infection of the joints or the tissue around them
- Impaired healing
- Inflammation of blood vessels in internal organs
- Leukaemia
- Melanoma (a type of skin cancer)
- Merkel cell carcinoma (a type of skin cancer)
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes)
- Scaly, peeling skin
- Immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- Pain and discolouration in the fingers or toes
- Taste disturbances
- Bladder disorders
- Kidney disorders
- Inflammation of the blood vessels in your skin which results in rash

Side effects of which the frequency is not known:
- A rare blood cancer affecting mostly young people (hepatosplenic T-cell lymphoma)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Simponi

- 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 label and 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.
- Keep the pre-filled syringe in the outer carton in order to protect it from light.
- This medicine can also be stored out of the refrigerator at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not beyond the original expiry date printed on the carton. Write the new expiry date on the carton including day/month/year (no more than 30 days after the medicine is removed from the refrigerator). Do not return this medicine to refrigerator if it has reached room temperature. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not use this medicine if you notice that the liquid is not a clear to light yellow colour, cloudy, or contains foreign particles.
- Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Simponi contains
The active substance is golimumab. One 1 mL pre-filled syringe contains 100 mg of golimumab.

The other ingredients are sorbitol (E420), histidine, histidine hydrochloride monohydrate, polysorbate 80 (E433) and water for injections. For more information on sorbitol (E420) and polysorbate 80 (E433), see Section 2.

What Simponi looks like and contents of the pack
Simponi is supplied as solution for injection in a single-use pre-filled syringe Simponi is available in packs containing 1 pre-filled syringe and multipacks containing 3 (3 packs of 1) pre-filled syringes. Not all pack sizes may be marketed.

The solution is clear to slightly opalescent (having a pearl-like shine), colourless to light yellow and may contain a few small translucent or white particles of protein. Do not use Simponi if the solution is discoloured, cloudy or you can see foreign particles in it.

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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

INSTRUCTIONS FOR USE

If you would like to self inject Simponi, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your doctor, nurse or pharmacist to schedule a training session.

In these instructions:
1. Preparing for use of the pre-filled syringe
2. Choosing and preparing the injection site
3. Injecting the medicine
4. After the injection

The diagram below (see figure 1) shows what the pre-filled syringe looks like.

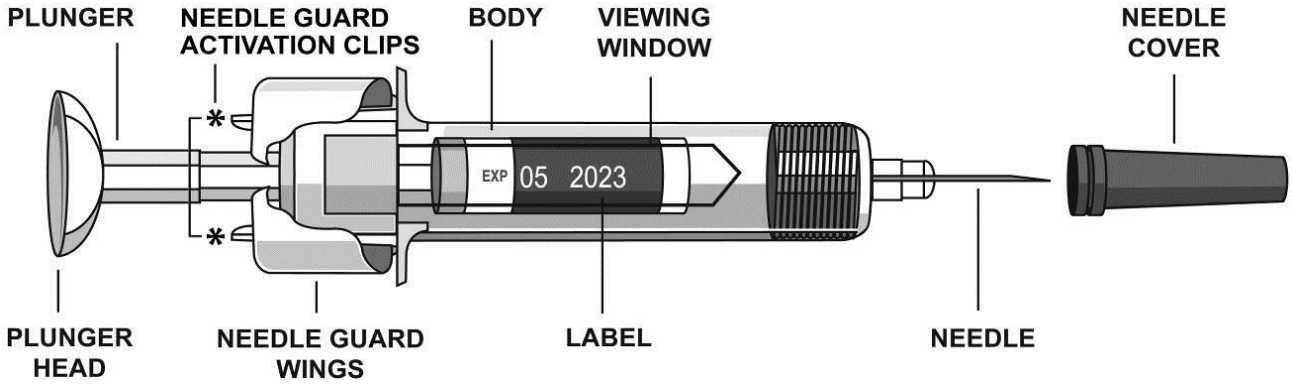


Figure 1

1. Preparing for use of the pre-filled syringe

Hold the pre-filled syringe by the body of the pre-filled syringe

- Do not hold by the plunger head, plunger, needle guard wings, or needle cover.
- Do not pull back on the plunger at any time.
- Do not shake the pre-filled syringe at any time.
- Do not remove the needle cover from the pre-filled syringe until instructed to do so.
- Do not touch the needle guard activation clips (as indicated by asterisks * in figure 1) to prevent prematurely covering the needle with the needle guard.

Check the number of pre-filled syringes
Check the pre-filled syringes to make sure
- the number of pre-filled syringes and strength is correct
  - If your dose is 100 mg, you will get one 100 mg pre-filled syringe
  - If your dose is 200 mg, you will get two 100 mg pre-filled syringes and you will need to give yourself two injections. Choose different sites for these injections and give the injections one right after the other.

Check expiry date (see figure 2)
- Check the expiry date printed or written on the carton.
- Check the expiry date (as indicated by "EXP") on the label by looking through the viewing window located within the body of the pre-filled syringe.
- If you cannot see the expiry date through the viewing window, hold the pre-filled syringe by its body and rotate the needle cover to line up the expiry date to the viewing window.

Do not use the pre-filled syringe if the expiry date has passed. The printed expiry date refers to the last day of the month. Please contact your doctor or pharmacist for assistance.

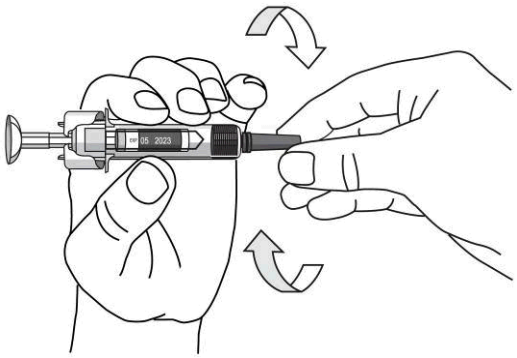


Figure 2

Wait 30 minutes to allow pre-filled syringe to reach room temperature

- To ensure proper injection, allow the pre-filled syringe to sit at room temperature outside the box for 30 minutes, out of the reach of children.

Do not warm the pre-filled syringe in any other way (for example, do not warm it in a microwave or in hot water).
Do not remove the pre-filled syringe's needle cover while allowing it to reach room temperature.

Get the rest of your equipment ready

While you are waiting you can get the rest of your equipment ready, including an alcohol swab, a cotton ball or gauze and a sharps container.

Check the liquid in the pre-filled syringe

- Hold the pre-filled syringe by its body with the covered needle pointing downward.
- Look at the liquid through the viewing window of the pre-filled syringe and make sure that it is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow. The solution can be used if it contains a few small translucent or white particles of protein.
- If you cannot see the liquid through the viewing window, hold the pre-filled syringe by its body and rotate the needle cover to line up the liquid to the viewing window (see figure 2).

Do not use the pre-filled syringe if the liquid is the wrong colour, cloudy, or contains larger particles. If this happens, talk to your doctor or pharmacist.

2. Choosing and preparing the injection site (see figure 3)

- You usually inject the medicine into the front of the middle thighs.
- You can also use the lower stomach (abdomen) below the belly button, except for approximately the 5 cm area directly underneath the belly button.
- Do not inject into areas where the skin is tender, bruised, red, scaly, hard or has scars or stretch marks.
- If multiple injections are required for a single administration, the injections should be administered at different sites on the body.

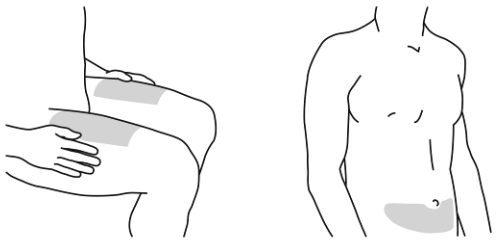


Figure 3

Injection site selection for caregivers (see figure 4)

- If a caregiver is giving you the injection, they can also use the outer area of the upper arms.
- Again, all sites mentioned can be used regardless of your body type or size.

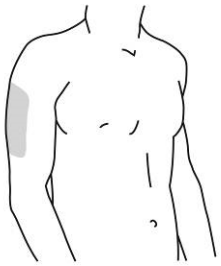


Figure 4

Preparing injection site

- Wash your hands thoroughly with soap and warm water.
- Wipe the injection site with an alcohol swab.
- Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Do not touch this area again before giving the injection.

3. Injecting the medicine

The needle cover should not be removed until you are ready to inject the medicine. The medicine should be injected within 5 minutes after the needle cover has been removed.

Do not touch the plunger during needle cover removal.

Remove the needle cover (see figure 5)

- When you are ready to inject, hold the body of the pre-filled syringe with one hand.
- Pull the needle cover straight off and throw it away after your injection. Do not touch the plunger while you do this.
- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed.
- Inject the dose promptly after removing the needle cover.

Do not touch the needle or allow it to touch any surface.
Do not use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist.

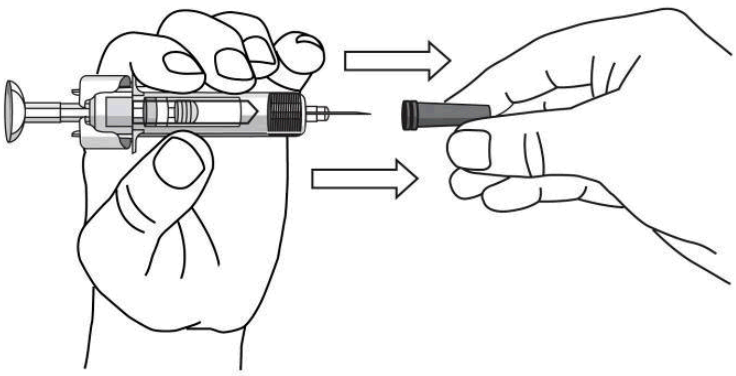


Figure 5

Position the pre-filled syringe to inject

- Hold the body of the pre-filled syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the area of skin that you previously cleaned. Hold firmly.

Do not pull back on the plunger at any time.

Inject the medicine

- Place the needle at approximately a 45-degree angle to the pinched skin. In a single and swift motion, insert the needle through the skin as far as it will go (see figure 6).

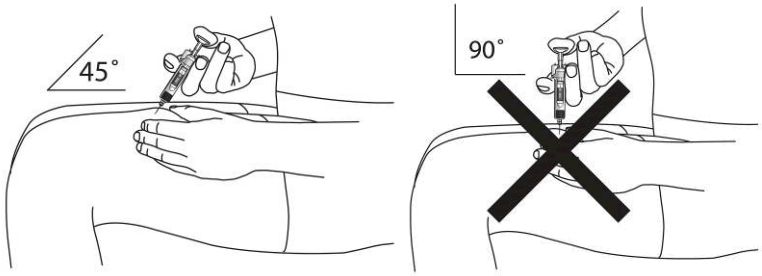


Figure 6

- Inject all of the medicine by pushing in the plunger until the plunger head is completely between the needle guard wings (see figure 7).



Figure 7

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see figure 8).

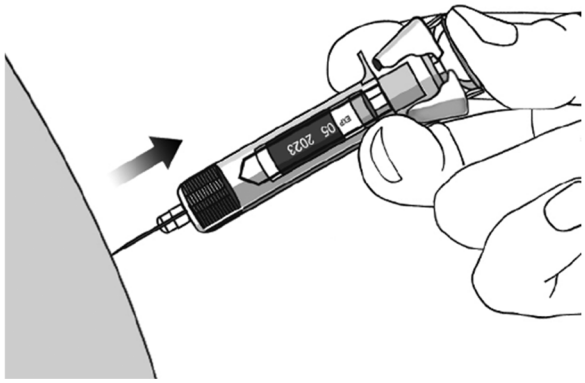


Figure 8

- Slowly take your thumb off the plunger head to allow the empty pre-filled syringe to move up until the entire needle is covered by the needle guard, as shown by the figure 9:

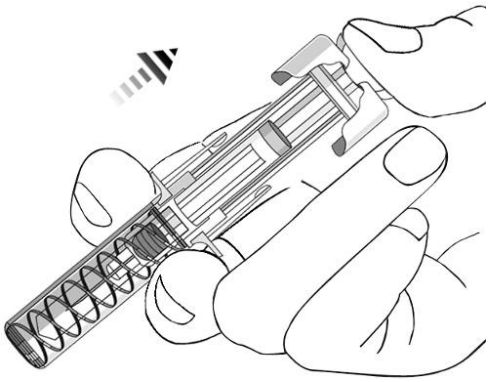


Figure 9

4. After the injection

Use a cotton ball or gauze

- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds.
- You may cover the injection site with a small adhesive bandage, if necessary.

Do not rub your skin.

Throw the pre-filled syringe away (see figure 10)

- Place your pre-filled syringe in a sharps container straight away. Make sure you dispose of the bin as instructed by your doctor or nurse.

Do not attempt to recap the needle.
Do not ever re-use a pre-filled syringe, for your safety and health and for the safety of others.

If you feel that something has gone wrong with the injection or if you are not sure, talk to your doctor or pharmacist.

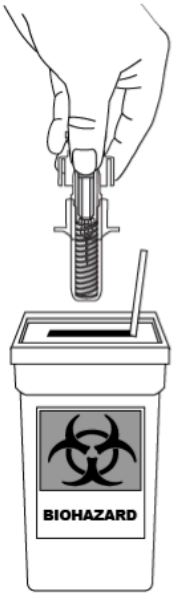


Figure 10