ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Teriflunomide Mylan 14 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 14 mg of teriflunomide.

Excipient(s) with known effect

Each tablet contains 85.4 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pale blue to pastel blue coloured, round, biconvex, film-coated tablets debossed with 'T' on one side and '1' on the other side, approximately 7.6 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Teriflunomide Mylan is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (please refer to section 5.1 for important information on the population for which efficacy has been established).

4.2 Posology and method of administration

The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis.

Posology

Adults
In adults, the recommended dose of teriflunomide is 14 mg once daily.

Paediatric population (10 years and older)
In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:
- Paediatric patients with body weight > 40 kg: 14 mg once daily.
- Paediatric patients with body weight ≤ 40 kg: 7 mg once daily.

Paediatric patients who reach a stable body weight above 40 kg should be switched to 14 mg once daily.

Teriflunomide Mylan is only available as 14 mg film-coated tablets. Thus, it is not possible to administer Teriflunomide Mylan to patients that require less than a full 14 mg dose. If an alternate dose is required, other teriflunomide products offering such an option should be used.

Special populations

Elderly population
Teriflunomide should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy.

Renal impairment
No dose adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis.
Patients with severe renal impairment undergoing dialysis were not evaluated. Teriflunomide is contraindicated in this population (see section 4.3).

Hepatic impairment
No dose adjustment is necessary for patients with mild and moderate hepatic impairment.
Teriflunomide is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population (less than 10 years of age)
The safety and efficacy of teriflunomide in children aged below 10 years have not been established. No data are available.

Method of administration

The film-coated tablets are for oral use. The tablets should be swallowed whole with some water. They can be taken with or without food.

4.3 Contraindications

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

Patients with severe hepatic impairment (Child-Pugh class C).

Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/l (see section 4.6). Pregnancy must be excluded before start of treatment (see section 4.6).

Breast-feeding women (see section 4.6).

Patients with severe immunodeficiency states, e.g. acquired immunodeficiency syndrome (AIDS).

Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia.

Patients with severe active infection until resolution (see section 4.4).

Patients with severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group.

Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.

4.4 Special warnings and precautions for use

Monitoring

Before treatment
Before starting treatment with teriflunomide the following should be assessed:
- Blood pressure
- Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)
- Complete blood cell count including differential white blood cell and platelet count.

During treatment
During treatment with teriflunomide the following should be monitored:

- Blood pressure
  - Check periodically
- Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)
  - Liver enzymes should be assessed at least every four weeks during the first 6 months of treatment, and regularly thereafter.
  - Consider additional monitoring when Teriflunomide Mylan is given in patients with pre-existing liver disorders, given with other potentially hepatotoxic drugs or as indicated by clinical signs and symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Liver enzymes should be assessed every two weeks during the first 6 months of treatment, and at least every 8 weeks thereafter for at least 2 years from initiation of treatment.
  - For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly.
- Complete blood cell counts should be performed based on clinical signs and symptoms (e.g. infections) during treatment.

Accelerated elimination procedure

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide (see sections 4.6 and 5.2 for procedural details).

Hepatic effects

Elevations of liver enzymes have been observed in patients receiving teriflunomide (see section 4.8). These elevations occurred mostly within the first 6 months of treatment.

Cases of drug-induced liver injury (DILI) have been observed during treatment with teriflunomide, sometimes life-threatening. Most cases of DILI occurred with time to onset of several weeks or several months after treatment initiation of teriflunomide, but DILI can also occur with prolonged use.
The risk for liver enzyme increases and DILI with teriflunomide might be higher in patients with pre-existing liver disorder, concomitant treatment with other hepatotoxic drugs, and/or consumption of substantial quantities of alcohol. Patients should therefore be closely monitored for signs and symptoms of liver injury.

Teriflunomide therapy should be discontinued and accelerated elimination procedure considered if liver injury is suspected. If elevated liver enzymes (greater than 3-fold ULN) are confirmed, teriflunomide therapy should be discontinued.

In case of treatment discontinuation, liver tests should be pursued until normalisation of transaminase levels.

Hypoproteinaemia

Since teriflunomide is highly protein bound and as the binding is dependent upon the concentrations of albumin, unbound plasma teriflunomide concentrations are expected to be increased in patients with hypoproteinaemia, e.g. in nephrotic syndrome. Teriflunomide should not be used in patients with conditions of severe hypoproteinaemia.

Blood pressure

Elevation of blood pressure may occur during treatment with teriflunomide (see section 4.8). Blood pressure must be checked before the start of teriflunomide treatment and periodically thereafter. Blood pressure elevation should be appropriately managed before and during treatment with teriflunomide.

Infections

Initiation of treatment with teriflunomide should be delayed in patients with severe active infection until resolution.
In placebo-controlled studies, no increase in serious infections was observed with teriflunomide (see section 4.8).
Cases of herpes virus infections, including oral herpes and herpes zoster, have been reported with teriflunomide (see section 4.8), with some of them being serious, including herpetic meningoencephalitis and herpes dissemination. They may occur at any time during treatment.
Based on the immunomodulatory effect of teriflunomide, if a patient develops any serious infection, suspending treatment with teriflunomide should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Due to the prolonged half-life, accelerated elimination with cholestyramine or charcoal may be considered.
Patients receiving teriflunomide should be instructed to report symptoms of infections to a physician.
Patients with active acute or chronic infections should not start treatment with teriflunomide until the infection(s) is resolved.
The safety of teriflunomide in individuals with latent tuberculosis infection is unknown, as tuberculosis screening was not systematically performed in clinical studies. Patients who tested positive in tuberculosis screening should be treated by standard medical practice prior to therapy.

Respiratory reactions

Interstitial lung disease (ILD) as well as cases of pulmonary hypertension have been reported with teriflunomide in the post-marketing setting.
The risk might be increased in patients with a history of ILD.

ILD may occur acutely at any time during therapy with a variable clinical presentation.
ILD may be fatal. New onset or worsening pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. If discontinuation of the medicinal product is necessary, initiation of an accelerated elimination procedure should be considered.

Haematological effects

A mean decrease less than 15% from baseline affecting white blood cell count has been observed (see section 4.8). As a precaution, a recent complete blood cell count, including differential white blood cell count and platelets, should be available before the initiation of treatment and the complete blood cell count should be assessed during therapy as indicated by clinical signs and symptoms (e.g., infections).

In patients with pre-existing anaemia, leucopenia, and /or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of haematological disorders is increased. If such effects occur, the accelerated elimination procedure (see above) to reduce plasma levels of teriflunomide should be considered.
In cases of severe haematological reactions, including pancytopenia, teriflunomide and any concomitant myelosuppressive treatment must be discontinued and a teriflunomide accelerated elimination procedure should be considered.

Skin reactions

Cases of serious skin reactions, sometimes fatal including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with teriflunomide.

If skin and /or mucosal reactions (ulcerative stomatitis) are observed which raise the suspicion of severe generalised major skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis-Lyell's syndrome or drug reaction with eosinophilia and systemic symptoms), teriflunomide and any other possibly associated treatment must be discontinued, and an accelerated procedure initiated immediately. In such cases patients should not be re-exposed to teriflunomide (see section 4.3).

New onset of psoriasis (including pustular psoriasis) and worsening of pre-existing psoriasis have been reported during the use of teriflunomide. Treatment withdrawal and initiation of an accelerated elimination procedure may be considered taking into account patient's disease and medical history.

Peripheral neuropathy

Cases of peripheral neuropathy have been reported in patients receiving teriflunomide (see section 4.8). Most patients improved after discontinuation of teriflunomide. However, there was a wide variability in final outcome, i.e. in some patients the neuropathy resolved and some patients had persistent symptoms. If a patient taking teriflunomide develops a confirmed peripheral neuropathy, discontinuing teriflunomide therapy and performing the accelerated elimination procedure should be considered.

Vaccination

Two clinical studies have shown that vaccinations to inactivated neoantigen (first vaccination) or recall antigen (re-exposure) were safe and effective during teriflunomide treatment. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.

Immunosuppressive or immunomodulating therapies

As leflunomide is the parent compound of teriflunomide, co-administration of teriflunomide with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies used for treatment of MS has not been evaluated. Safety studies, in which teriflunomide was concomitantly administered with interferon beta or with glatiramer acetate for up to one year did not reveal any specific safety concerns, but a higher adverse reaction rate as compared to teriflunomide monotherapy was observed. The long-term safety of these combinations in the treatment of multiple sclerosis has not been established.

Switching to or from teriflunomide

Based on the clinical data related to concomitant administration of teriflunomide with interferon beta or with glatiramer acetate, no waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate or when starting interferon beta or glatiramer acetate, after teriflunomide.

Due to the long half-life of natalizumab, concomitant exposure, and thus concomitant immune effects, could occur for up to 2-3 months following discontinuation of natalizumab if teriflunomide was immediately started. Therefore, caution is required when switching patients from natalizumab to teriflunomide.

Based on the half-life of fingolimod, a 6-week interval without therapy is needed for clearance from the circulation and a 1 to 2-month period is needed for lymphocytes to return to normal range following discontinuation of fingolimod. Starting teriflunomide during this interval will result in concomitant exposure to fingolimod. This may lead to an additive effect on the immune system and caution is, therefore, indicated.

In MS patients, the median $t_{1/2z}$ was approximately 19 days after repeated doses of 14 mg. If a decision is made to stop treatment with teriflunomide, during the interval of 5 half-lives (approximately 3.5 months although may be longer in some patients), starting other therapies will result in

concomitant exposure to teriflunomide. This may lead to an additive effect on the immune system and caution is, therefore, indicated.

Interference with determination of ionised calcium levels

The measurement of ionised calcium levels might show falsely decreased values under treatment with leflunomide and/or teriflunomide (the active metabolite of leflunomide) depending on the type of ionised calcium analyser used (e.g. blood gas analyser). Therefore, the plausibility of observed decreased ionised calcium levels needs to be questioned in patients under treatment with leflunomide or teriflunomide. In case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration.

Paediatric population

Pancreatitis
In the paediatric clinical trial, cases of pancreatitis, some acute, have been observed in patients receiving teriflunomide (see section 4.8). Clinical symptoms included abdominal pain, nausea and/or vomiting. Serum amylase and lipase were elevated in these patients. The time to onset ranged from a few months up to three years. Patients should be informed of the characteristic symptoms of pancreatitis. If pancreatitis is suspected, pancreatic enzymes and related laboratory parameters should be obtained. If pancreatitis is confirmed, teriflunomide should be discontinued and an accelerated elimination procedure should be initiated (see section 5.2).

Excipients with known effect

Lactose
Teriflunomide Mylan tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions of other substances on teriflunomide

The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway.

Potent cytochrome P450 (CYP) and transporter inducers
Co-administration of repeated doses (600 mg once daily for 22 days) of rifampicin (a CYP2B6, 2C8, 2C9, 2C19, 3A inducer), as well as an inducer of the efflux transporters P-glycoprotein [P-gp] and breast cancer resistant protein [BCRP] with teriflunomide (70 mg single dose) resulted in an approximately 40% decrease in teriflunomide exposure. Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin and St John’s Wort should be used with caution during the treatment with teriflunomide.

Cholestyramine or activated charcoal
It is recommended that patients receiving teriflunomide are not treated with cholestyramine or activated charcoal because this leads to a rapid and significant decrease in plasma concentration unless an accelerated elimination is desired. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of teriflunomide.

Pharmacokinetic interactions of teriflunomide on other substances

Effect of teriflunomide on CYP2C8 substrate: repaglinide
There was an increase in mean repaglinide C_{max} and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 *in vivo*. Therefore, medicinal products metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during treatment with teriflunomide.

Effect of teriflunomide on oral contraceptives: 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel
There was an increase in mean ethinylestradiol C_{max} and AUC_{0-24} (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC_{0-24} (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide. While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment used in combination with teriflunomide.

Effect of teriflunomide on CYP1A2 substrate: caffeine
Repeated doses of teriflunomide decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 *in vivo*. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetine, alosetron, theophylline and tizanidine) should be used with caution during treatment with teriflunomide, as it could lead to the reduction of the efficacy of these medicinal products.

Effect of teriflunomide on warfarin
Repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin, indicating that teriflunomide is not an inhibitor or an inducer of CYP2C9. However, a 25% decrease in peak international normalised ratio (INR) was observed when teriflunomide was co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered with teriflunomide, close INR follow-up and monitoring is recommended.

Effect of teriflunomide on organic anion transporter 3 (OAT3) substrates
There was an increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of OAT3 *in vivo*. Therefore, when teriflunomide is co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.

Effect of teriflunomide on BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates
There was an increase in mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively), following repeated doses of teriflunomide. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. For rosuvastatin, a dose reduction by 50% is recommended for co-administration with teriflunomide. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration of teriflunomide should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

4.6 Fertility, pregnancy and lactation

Use in males

The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low (see section 5.3).

Pregnancy

There are limited amount of data from the use of teriflunomide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Teriflunomide may cause serious birth defects when administered during pregnancy. Teriflunomide is contraindicated in pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. During this period women should discuss any plans to stop or change contraception with the treating physician. Female children and/or parents/caregivers of female children should be informed about the need to contact the treating physician once the female child under teriflunomide treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the foetus. Referral to a gynaecologist should be considered.

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must discontinue teriflunomide and notify the physician immediately for pregnancy testing, and if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of teriflunomide, by instituting the accelerated elimination procedure described below, at the first delay of menses, may decrease the risk to the foetus.
For women receiving teriflunomide treatment, who wish to become pregnant, the medicinal product should be stopped and an accelerated elimination procedure is recommended in order to more rapidly achieve concentration below 0.02 mg/l (see below).

If an accelerated elimination procedure is not used, teriflunomide plasma levels can be expected to be above 0.02 mg/l for an average of 8 months, however, in some patients it may take up to 2 years to reach plasma concentration below 0.02 mg/l. Therefore, teriflunomide plasma concentrations should be measured before a woman begins to attempt to become pregnant. Once the teriflunomide plasma concentration is determined to be below 0.02 mg/l, the plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l, no risk to the foetus is to be expected.
For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

Accelerated elimination procedure
After stopping treatment with teriflunomide:

- cholestyramine 8 g is administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated
- alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days.

However, also following either of the accelerated elimination procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation is required.
Both cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the accelerated elimination procedure with cholestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Breast-feeding

Animal studies have shown excretion of teriflunomide in milk. Teriflunomide is contraindicated during breast-feeding (see section 4.3).

Fertility

Results of studies in animals have not shown an effect on fertility (see section 5.3). Although human data are lacking, no effect on male and female fertility is anticipated.

4.7 Effects on ability to drive and use machines

Teriflunomide has no or negligible influence on the ability to drive and use machines.
In the case of adverse reactions such as dizziness, which has been reported with leflunomide, the parent compound, the patient's ability to concentrate and to react properly may be impaired. In such cases, patients should refrain from driving and using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions in the teriflunomide treated (7 mg and 14 mg) patients were: headache (17.8%, 15.7%), diarrhoea (13.1%, 13.6%) increased ALT (13%, 15%), nausea (8%, 10.7%), and alopecia (9.8%, 13.5%). In general, headache, diarrhoea, nausea and alopecia, were mild to moderate, transient and infrequently led to treatment discontinuation.

Teriflunomide is the main metabolite of leflunomide. The safety profile of leflunomide in patients suffering from rheumatoid arthritis or psoriatic arthritis may be pertinent when prescribing teriflunomide in MS patients.

Tabulated list of adverse reactions

Teriflunomide was evaluated in a total of 2,267 patients exposed to teriflunomide (1,155 on teriflunomide 7 mg and 1,112 on teriflunomide 14 mg) once daily for a median duration of about 672 days in four placebo-controlled studies (1,045 and 1,002 patients for teriflunomide 7 mg and 14 mg, respectively) and one active comparator study (110 patients in each of the teriflunomide treatment groups) in adult patients with relapsing forms of MS (Relapsing Multiple Sclerosis, RMS).

Listed below are the adverse reactions reported with teriflunomide in placebo-controlled studies, reported for teriflunomide 7 mg or 14 mg from clinical studies in adult patients. Frequencies were defined 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 ranked in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Influenza, Upper respiratory tract infection, Urinary tract infection, Bronchitis, Sinusitis, Pharyngitis, Cystitis, Gastroenteritis viral, Herpes virus infections[b], Tooth infection, Laryngitis, Tinea pedis	Severe infections including sepsis[a]			
Blood and lymphatic system disorders		Neutropenia[b], Anaemia	Mild thrombocytopenia (platelets < 100 G/l)			
Immune system disorders		Mild allergic reactions	Hyper-sensitivity reactions			

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
			(immediate or delayed) including anaphylaxis and angioedema			
Metabolism and nutrition disorders			Dyslipidaemia			
Psychiatric disorders		Anxiety				
Nervous system disorders	Headache	Paraesthesia, Sciatica, Carpal tunnel syndrome	Hyperaesthesia, Neuralgia, Peripheral neuropathy			
Cardiac disorders		Palpitations				
Vascular disorders		Hypertension[b]				
Respiratory, thoracic and mediastinal disorders			Interstitial lung disease			Pulmonary hypertension
Gastrointestinal disorders	Diarrhoea, Nausea	Pancreatitis[b,c], Abdominal pain upper, Vomiting, Toothache	Stomatitis, Colitis			
Hepatobiliary disorders	Alanine aminotransferase (ALT) increase[b]	Gamma-glutamyltransferase (GGT) increase[b], Aspartate aminotransferase increase[b]		Acute hepatitis		Drug-induced liver injury (DILI)
Skin and subcutaneous tissue disorders	Alopecia	Rash, Acne	Nail disorders, Psoriasis (including pustular)[a,b], Severe skin reactions[a]			
Musculoskeletal and connective tissue disorders		Musculoskeletal pain, Myalgia, Arthralgia				
Renal and urinary disorders		Pollakiuria				
Reproductive system and breast disorders		Menorrhagia				
General disorders and		Pain, Asthenia[a]				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
administration site conditions						
Investigations		Weight decrease, Neutrophil count decrease[b], White blood cell count decrease[b], Blood creatine phosphokinase increased				
Injury, poisoning and procedural complications			Post-traumatic pain			

[a]: please refer to the detailed description section
[b]: see section 4.4
[c]: frequency is 'common' in children based on a controlled clinical study in paediatrics; frequency is 'uncommon' in adults

Description of selected adverse reactions

Alopecia
Alopecia was reported as hair thinning, decreased hair density, hair loss, associated or not with hair texture change, in 13.9% of patients treated with 14 mg teriflunomide versus 5.1% in patients treated with placebo. Most cases were described as diffuse or generalised over the scalp (no complete hair loss reported) and occurred most often during the first 6 months and with resolution in 121 of 139 (87.1%) patients treated with teriflunomide 14 mg. Discontinuation because of alopecia was 1.3% in the teriflunomide 14 mg group, versus 0.1% in the placebo group.

Hepatic effects
During placebo-controlled studies in adult patients the following was detected:

ALT increase (based on laboratory data) according to baseline status – Safety population in placebo-controlled studies		
	Placebo (N=997)	**Teriflunomide 14 mg (N=1002)**
> 3 ULN	66/994 (6.6%)	80/999 (8.0%)
> 5 ULN	37/994 (3.7%)	31/999 (3.1%)
> 10 ULN	16/994 (1.6%)	9/999 (0.9%)
> 20 ULN	4/994 (0.4%)	3/999 (0.3%)
ALT > 3 ULN and TBILI > 2 ULN	5/994 (0.5%)	3/999 (0.3%)

Mild increases in transaminase, ALT below or equal to 3-fold ULN were more frequently seen in teriflunomide-treated groups as compared to placebo. The frequency of elevations above 3-fold ULN and higher was balanced across treatment groups. These elevations in transaminase occurred mostly within the first 6 months of treatment and were reversible after treatment cessation. The recovery time varied between months and years.

Blood pressure effects
In placebo-controlled studies in adult patients the following was established:
- systolic blood pressure was > 140 mm Hg in 19.9% of patients receiving 14 mg/day teriflunomide as compared to 15.5% receiving placebo;

- systolic blood pressure was > 160 mm Hg in 3.8% of patients receiving 14 mg/day teriflunomide as compared to 2.0% receiving placebo;
- diastolic blood pressure was > 90 mm Hg in 21.4% of patients receiving 14 mg/day teriflunomide as compared to 13.6% receiving placebo.

Infections
In placebo-controlled studies in adult patients, no increase in serious infections was observed with teriflunomide 14 mg (2.7%) as compared to placebo (2.2%). Serious opportunistic infections occurred in 0.2% of each group. Severe infections including sepsis, sometimes fatal have been reported post-marketing.

Haematological effects
A mean decrease affecting white blood cell (WBC) count (< 15% from baseline levels, mainly neutrophil and lymphocytes decrease) was observed in placebo-controlled trials with teriflunomide in adult patients, although a greater decrease was observed in some patients. The decrease in mean count from baseline occurred during the first 6 weeks then stabilised over time while on-treatment but at decreased levels (less than a 15% decrease from baseline). The effect on red blood cell (RBC) (< 2%) and platelet counts (< 10%) was less pronounced.

Peripheral neuropathy
In placebo-controlled studies in adult patients, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), was reported more frequently in patients taking teriflunomide than in patients taking placebo. In the pivotal, placebo-controlled studies, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.9% (17 patients out of 898) on 14 mg of teriflunomide, compared with 0.4% (4 patients out of 898) on placebo. Treatment was discontinued in 5 patients with peripheral neuropathy on teriflunomide 14 mg. Recovery following treatment discontinuation was reported in 4 of these patients.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
There does not appear to be an increased risk of malignancy with teriflunomide in the clinical trial experience. The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some other agents that affect the immune system (class effect).

Severe skin reactions
Cases of severe skin reactions have been reported with teriflunomide post-marketing (see section 4.4).

Asthenia
In placebo-controlled studies in adult patients, frequencies for asthenia were 2.0%, 1.6% and 2.2% in the placebo, teriflunomide 7 mg and teriflunomide 14 mg group, respectively.

Psoriasis
In placebo-controlled studies, frequencies for psoriasis were 0.3%, 0.3% and 0.4% in the placebo, teriflunomide 7 mg and teriflunomide 14 mg group, respectively.

Gastrointestinal disorders
Pancreatitis has been reported infrequently in the post-marketing setting with teriflunomide in adults, including cases of necrotising pancreatitis and pancreatic pseudocyst. Pancreatic events may occur at any time during treatment with teriflunomide, which may lead to hospitalisation and/or require corrective treatment.

Paediatric population

The observed safety profile in paediatric patients (from 10 to 17 years-old) receiving teriflunomide daily was overall similar to that seen in adult patients. However, in the paediatric study (166 patients: 109 in the teriflunomide group and 57 in the placebo group), cases of pancreatitis were reported in 1.8% (2/109) of the teriflunomide-treated patients compared to none in the placebo group, in the double-blind phase. One of these events led to hospitalisation and required corrective treatment. In

paediatric patients treated with teriflunomide in the open-label phase of the study, 2 additional cases of pancreatitis (one was reported as a serious event, the other was a nonserious event of mild intensity) and one case of serious acute pancreatitis (with pseudo-papilloma), were reported. In two of these 3 patients, pancreatitis led to hospitalisation. Clinical symptoms included abdominal pain, nausea and/ or vomiting and serum amylase and lipase were elevated in these patients. All patients recovered after treatment discontinuation and accelerated elimination procedure (see section 4.4) and corrective treatment.

The following adverse reactions were more frequently reported in the paediatric population than in the adult
population:

- Alopecia was reported in 22.0% of patients treated with teriflunomide versus 12.3% in patients treated with placebo.
- Infections were reported in 66.1% of patients treated with teriflunomide versus 45.6% in patients treated with placebo. Among them, nasopharyngitis and upper respiratory tract infections were more frequently reported with teriflunomide.
- CPK increase was reported in 5.5% of patients treated with teriflunomide versus 0% in patients treated with placebo. The majority of the cases were associated with documented physical exercise.
- Paraesthesia was reported in 11.0% of patients treated with teriflunomide versus 1.8% in patients treated with placebo.
- Abdominal pain was reported in 11.0% of patients treated with teriflunomide versus 1.8% in patients treated with placebo.

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

Symptoms

There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily was administered up to 14 days in healthy subjects. The adverse reactions were consistent with the safety profile for teriflunomide in MS patients.

Management

In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination. The recommended elimination procedure is cholestyramine 8 g three times a day for 11 days. If this is not well tolerated, cholestyramine 4 g three times a day for 11 days can be used. Alternatively, when cholestyramine is not available, activated charcoal 50 g twice a day for 11 days may also be used. In addition, if required for tolerability reasons, administration of cholestyramine or activated charcoal does not need to occur on consecutive days (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Selective immunosuppressants, ATC Code: L04AA31

Mechanism of action

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which functionally connects with the respiratory chain. As a consequence of the inhibition, teriflunomide generally reduces the proliferation of rapidly dividing cells that depend on *de novo* synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.

Pharmacodynamic effects

Immune system
Effects on immune cell numbers in the blood: In the placebo-controlled studies, teriflunomide 14 mg once a day led to a mild mean reduction in lymphocyte count, of less than 0.3 x 10^9/l, which occurred over the first 3 months of treatment and levels were maintained until the end of the treatment.

Potential to prolong the QT interval
In a placebo-controlled thorough QT study performed in healthy subjects, teriflunomide at mean steady-state concentrations did not show any potential for prolonging the QTcF interval compared with placebo: the largest time matched mean difference between teriflunomide and placebo was 3.45 ms with the upper bound of the 90% CI being 6.45 ms.

Effect on renal tubular functions
In the placebo-controlled studies, mean decreases in serum uric acid at a range of 20 to 30% were observed in patients treated with teriflunomide compared to placebo. Mean decrease in serum phosphorus was around 10% in the teriflunomide group compared to placebo. These effects are considered to be related to increase in renal tubular excretion and not related to changes in glomerular functions.

Clinical efficacy and safety

The efficacy of teriflunomide was demonstrated in two placebo-controlled studies, the TEMSO and the TOWER study, that evaluated once daily doses of teriflunomide 7 mg and 14 mg in adult patients with RMS.

A total of 1,088 patients with RMS were randomised in TEMSO to receive 7 mg (n=366) or 14 mg (n=359) of teriflunomide or placebo (n= 363) for 108 weeks duration. All patients had a definite diagnosis of MS (based on McDonald criteria (2001)), exhibited a relapsing clinical course, with or without progression, and experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ≤ 5.5. The mean age of the study population was 37.9 years. The majority of patients had relapsing–remitting multiple sclerosis (91.5%), but a subgroup of patients had secondary progressive (4.7%) or progressive relapsing multiple sclerosis (3.9%). The mean number of relapses within the year before study inclusion was 1.4 with 36.2% of patients having gadolinium-enhancing lesions at baseline. The median EDSS score at baseline was 2.50**;** 249 patients (22.9%) had an EDSS score › 3.5 at baseline. The mean duration of disease, since first symptoms, was 8.7 years. A majority of patients (73%) had not received disease-modifying therapy during the 2 years before study entry. The study results are shown in Table 1.

Long term follow-up results from TEMSO long term extension safety study (overall median treatment duration approximately 5 years, maximum treatment duration approximately 8.5 years) did not present any new or unexpected safety findings.

A total of 1,169 patients with RMS were randomised in TOWER to receive 7 mg (n=408) or 14 mg (n=372) of teriflunomide or placebo (n= 389) for a variable treatment duration ending at 48 weeks after last patient randomised. All patients had a definite diagnosis of MS (based on McDonald criteria (2005)), exhibited a relapsing clinical course, with or without progression, and experienced at least 1

relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ≤ 5.5.
The mean age of the study population was 37.9 years. The majority of patients had relapsing–remitting multiple sclerosis (97.5%), but a subgroup of patients had secondary progressive (0.8%) or progressive relapsing multiple sclerosis (1.7%). The mean number of relapses within the year before study inclusion was 1.4. Gadolinium-enhancing lesions at baseline: no data. The median EDSS score at baseline was 2.50; 298 patients (25.5%) had an EDSS score › 3.5 at baseline. The mean duration of disease, since first symptoms, was 8.0 years. A majority of patients (67.2%) had not received disease-modifying therapy during the 2 years before study entry. The study results are shown in Table 1.

Table 1 - Main results (for the approved dose, ITT population)

	TEMSO-study		**TOWER-study**	
	Teriflunomide 14 mg	**Placebo**	**Teriflunomide 14 mg**	**Placebo**
N	**358**	**363**	**370**	**388**
Clinical Outcomes				
Annualised relapse rate	0.37	0.54	0.32	0.50
Risk difference ($CI_{95\%}$)	-0.17 (-0.26, -0.08)***		-0.18 (-0.27, -0.09)****	
Relapse-free $_{week\ 108}$	56.5%	45.6%	57.1%	46.8%
Hazard ratio ($CI_{95\%}$)	0.72 (0.58, 0.89) **		0.63 (0.50, 0.79) ****	
3-month Sustained Disability Progression $_{week\ 108}$	20.2%	27.3%	15.8%	19.7%
Hazard ratio ($CI_{95\%}$)	0.70 (0.51, 0.97)*		0.68 (0.47, 1.00) *	
6-month Sustained Disability Progression $_{week\ 108}$	13.8%	18.7%	11.7%	11.9%
Hazard ratio ($CI_{95\%}$)	0.75 (0.50, 1.11)		0.84 (0.53, 1.33)	
MRI endpoints			Not measured	
Change in BOD $_{week\ 108}$(1)	0.72	2.21		
Change relative to placebo	67%***			
Mean Number of Gd-enhancing lesions at week 108	0.38	1.18		
Change relative to placebo ($CI_{95\%}$)	-0.80 (-1.20, -0.39)****			
Number of unique active lesions/scan	0.75	2.46		
Change relative to placebo ($CI_{95\%}$)	69%, (59%, 77%)****			

**** $p < 0.0001$ *** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$ compared to placebo
(1) BOD: burden of disease: total lesion volume (T2 and T1 hypointense) in ml

Efficacy in patients with high disease activity:
A consistent treatment effect on relapses and time to 3-month sustained disability progression in a subgroup of patients in TEMSO (n= 127) with high disease activity was observed. Due to the design of the study, high disease activity was defined as 2 or more relapses in one year, and with one or more Gd-enhancing lesion on brain MRI. No similar subgroup analysis was performed in TOWER as no MRI data were obtained.
No data are available in patients who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or patients having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years.

TOPIC was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg for up to 108 weeks in patients with first clinical demyelinating event (mean age 32.1 years). The primary endpoint was time to a second clinical episode (relapse). A total of 618

patients were randomised to receive 7 mg (n=205) or 14 mg (n=216) of teriflunomide or placebo (n=197). The risk of a second clinical attack over 2 years was 35.9% in the placebo group and 24.0% in the teriflunomide 14 mg treatment group (hazard ratio: 0.57, 95% confidence interval: 0.38 to 0.87, p=0.0087). The results from the TOPIC study confirmed the efficacy of teriflunomide in RRMS (including early RRMS with first clinical demyelinating event and MRI lesions disseminated in time and space).

Teriflunomide effectiveness was compared to that of a subcutaneous interferon beta-1a (at the recommended dose of 44 µg three times a week) in 324 randomised patients in a study (TENERE) with minimum treatment duration of 48 weeks (maximum 114 weeks). The risk of failure (confirmed relapse or permanent treatment discontinuation whichever came first) was the primary endpoint. The number of patients with permanent treatment discontinuation in the teriflunomide 14 mg group was 22 out of 111 (19.8%), the reasons being adverse events (10.8%), lack of efficacy (3.6%), other reason (4.5%) and lost to follow-up (0.9%). The number of patients with permanent treatment discontinuation in the subcutaneous interferon beta-1a group was 30 out of 104 (28 .8%), the reasons being adverse events (21.2%), lack of efficacy (1.9%), other reason (4.8%) and poor compliance to protocol (1%). Teriflunomide 14 mg/day was not superior to interferon beta-1a on the primary endpoint: the estimated percentage of patients with treatment failure at 96 weeks using the Kaplan-Meier method was 41.1% versus 44.4% (teriflunomide 14 mg versus interferon beta-1a group, p=0.595).

Paediatric population

Children and adolescents (10 to 17 years of age)
Study EFC11759/TERIKIDS was an international double-blind, placebo-controlled study in paediatric patients aged 10 to 17 years with relapsing-remitting MS that evaluated once daily doses of teriflunomide (adjusted to reach an exposure equivalent to the dose of 14 mg in adults) for up to 96 weeks followed by an open-label extension. All patients had experienced at least 1 relapse over 1 year or at least 2 relapses over 2 years preceding the study. Neurological evaluations were performed at screening and every 24 weeks until the completion, and at unscheduled visits for suspected relapse. Patients with a clinical relapse or high MRI activity of at least 5 new or enlarging T2 lesions on 2 consecutive scans were switched prior to 96 weeks to the open-label extension to ensure active treatment. The primary endpoint was time to first clinical relapse after randomisation. Time to first confirmed clinical relapse or high MRI activity, whichever came first, was pre-defined as a sensitivity analysis because it includes both clinical and MRI conditions qualifying for switching into the open-label period.

A total of 166 patients were randomised at a 2:1 ratio to receive teriflunomide (n=109) or placebo (n=57). At entry, study patients had an EDSS score ≤ 5.5; the mean age was 14.6 years; the mean weight was 58.1 kg; the mean disease duration since diagnosis was 1.4 years; and the mean T1 Gd-enhancing lesions per MRI scan was 3.9 lesions at baseline. All patients had relapsing remitting MS with the median EDSS score of 1.5 at baseline. The mean treatment time was 362 days on placebo and 488 days on teriflunomide. Switching from the double-blind period to open-label treatment due to high MRI activity was more frequent than anticipated, and more frequent and earlier in the placebo group than in the teriflunomide group (26% on placebo, 13% on teriflunomide).

Teriflunomide reduced the risk of clinical relapse by 34% relative to placebo, without reaching statistical significance (p = 0.29) (Table 2). In the pre-defined sensitivity analysis, teriflunomide achieved a statistically significant reduction in the combined risk of clinical relapse or high MRI activity by 43% relative to placebo (p = 0.04) (Table 2).

Teriflunomide significantly reduced the number of new and enlarging T2 lesions per scan by 55% (p=0.0006) (post-hoc analysis also adjusted for baseline T2 counts: 34%, p=0.0446), and the number of Gadolinium-enhancing T1 lesions per scan by 75% (p<0.0001) (Table 2).

Table 2 - Clinical and MRI results of EFC11759/TERIKIDS

EFC11759 ITT population	Teriflunomide (N=109)	Placebo (N=57)
Clinical endpoints		
Time to first confirmed clinical relapse, Probability (95% CI) of confirmed relapse at Week 96 *Probability (95% CI) of confirmed relapse at Week 48*	 0.39 (0.29, 0.48) *0.30 (0.21, 0.39)*	 0.53 (0.36, 0.68) *0.39 (0.30, 0.52)*
Hazard Ratio (95% CI)	0.66 (0.39, 1.11)^	
Time to first confirmed clinical relapse or high MRI activity, Probability (95%CI) of confirmed relapse or high MRI activity at Week 96 *Probability (95%CI) of confirmed relapse or high MRI activity at Week 48*	 0.51 (0.41, 0.60) *0.38 (0.29, 0.47)*	 0.72 (0.58, 0.82) *0.56 (0.42, 0.68)*
Hazard Ratio (95% CI)	0.57 (0.37, 0.87)*	
Key MRI endpoints		
Adjusted number of new or enlarged T2 lesions, Estimate (95% CI) *Estimate (95% CI), post-hoc analysis also adjusted for baseline T2 counts*	 4.74 (2.12, 10.57) *3.57 (1.97, 6.46)*	 10.52 (4.71, 23.50) *5.37 (2.84, 10.16)*
Relative risk (95% CI) Relative risk (95% CI), *post-hoc analysis also adjusted for baseline T2 counts*	0.45 (0.29, 0.71)** *0.67 (0.45, 0.99)**	
Adjusted number of T1 Gd-enhancing lesions, Estimate (95% CI)	 1.90 (0.66, 5.49)	 7.51 (2.48, 22.70)
Relative risk (95% CI)	0.25 (0.13, 0.51)***	
^p≥0.05 compared to placebo, * p<0.05, ** p<0.001, *** p<0.0001 Probability was based on Kaplan-Meier estimator and Week 96 was the end of study treatment (EOT).		

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing teriflunomide in children from birth to less than 10 years in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Median time to reach maximum plasma concentrations occurs between 1 to 4 hours post-dose following repeated oral administration of teriflunomide, with high bioavailability (approximately 100%).

Food does not have a clinically relevant effect on teriflunomide pharmacokinetics.

From the mean predicted pharmacokinetic parameters calculated from the population pharmacokinetic (PopPK) analysis using data from healthy volunteers and MS patients, there is a slow approach to steady-state concentration (i.e., approximately 100 days (3.5 months) to attain 95% of steady-state concentrations) and the estimated AUC accumulation ratio is approximately 34-fold.

Distribution

Teriflunomide is extensively bound to plasma protein (> 99%), probably albumin and is mainly distributed in plasma. The volume of distribution is 11 l after a single intravenous (IV) administration.

However, this is most likely an underestimation since extensive organ distribution was observed in rats.

Biotransformation

Teriflunomide is moderately metabolised and is the only component detected in plasma. The primary biotransformation pathway for teriflunomide is hydrolysis with oxidation being a minor pathway. Secondary pathways involve oxidation, N-acetylation and sulfate conjugation.

Elimination

Teriflunomide is excreted in the gastrointestinal tract mainly through the bile as unchanged active substance and most likely by direct secretion. Teriflunomide is a substrate of the efflux transporter BCRP, which could be involved in direct secretion. Over 21 days, 60.1% of the administered dose is excreted via faeces (37.5%) and urine (22.6%). After the rapid elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in faeces). Based on individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, median $t_{1/2z}$ was approximately 19 days after repeated doses of 14 mg. After a single intravenous administration, the total body clearance of teriflunomide is 30.5 ml/h.

Accelerated elimination procedure: cholestyramine and activated charcoal
The elimination of teriflunomide from the circulation can be accelerated by administration of cholestyramine or activated charcoal, presumably by interrupting the reabsorption processes at the intestinal level. Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 8 g cholestyramine three times a day, 4 g cholestyramine three times a day or 50 g activated charcoal twice a day following cessation of teriflunomide treatment have shown that these regimens were effective in accelerating teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations, with cholestyramine being faster than charcoal. Following discontinuation of teriflunomide and the administration of cholestyramine 8 g three times a day, the plasma concentration of teriflunomide is reduced 52% at the end of day 1, 91% at the end of day 3, 99.2% at the end of day 7, and 99.9% at the completion of day 11. The choice between the 3 elimination procedures should depend on the patient's tolerability. If cholestyramine 8 g three times a day is not well-tolerated, cholestyramine 4 g three times a day can be used. Alternatively, activated charcoal may also be used (the 11 days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly).

Linearity/non-linearity

Systemic exposure increases in a dose proportional manner after oral administration teriflunomide from 7 to 14 mg.

Characteristics in specific groups of patients

Gender and elderly
Several sources of intrinsic variability were identified in healthy subjects and MS patients based on the PopPK analysis: age, body weight, gender, race, and albumin and bilirubin levels. Nevertheless, their impact remains limited ($\leq$ 31%).

Hepatic impairment
Mild and moderate hepatic impairment had no impact on the pharmacokinetic of teriflunomide. Therefore, no dose adjustment is anticipated in mild and moderate hepatic-impaired patients. However, teriflunomide is contraindicated in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Renal impairment
Severe renal impairment had no impact on the pharmacokinetic of teriflunomide. Therefore, no dose adjustment is anticipated in mild, moderate and severe renal-impaired patients.

Paediatric population
In paediatric patients with body weight > 40 kg treated with 14 mg once daily, steady state exposures were in the range observed in adult patients treated with the same dosing regimen.
In paediatric patients with body weight ≤ 40 kg treatment with 7 mg once daily (based on limited clinical data and simulations) led to steady state exposures in the range observed in adult patients treated with 14 mg once daily.
Observed steady state trough concentrations were highly variable between individuals, as observed for adult MS patients.

5.3 Preclinical safety data

Repeated-dose toxicity

Repeated oral administration of teriflunomide to mice, rats and dogs for up to 3, 6, and 12 months, respectively, revealed that the major targets of toxicity were the bone marrow, lymphoid organs, oral cavity/ gastrointestinal tract, reproductive organs, and pancreas. Evidence of an oxidative effect on red blood cells was also observed. Anaemia, decreased platelet counts and effects on the immune system, including leucopenia, lymphopenia and secondary infections, were related to the effects on the bone marrow and/or lymphoid organs. The majority of effects reflect the basic mode of action of the compound (inhibition of dividing cells). Animals are more sensitive to the pharmacology, and therefore toxicity, of teriflunomide than humans. As a result, toxicity in animals was found at exposures equivalent or below human therapeutic levels.

Genotoxic and carcinogenic potential

Teriflunomide was not mutagenic *in vitro* or clastogenic *in vivo*. Clastogenicity observed *in vitro* was considered to be an indirect effect related to nucleotide pool imbalance resulting from the pharmacology of DHO-DH inhibition. The minor metabolite TFMA (4-trifluoromethylaniline) caused mutagenicity and clastogenicity *in vitro* but not *in vivo*.

No evidence of carcinogenicity was observed in rats and mice.

Reproduction toxicity

Fertility was unaffected in rats despite adverse effects of teriflunomide on male reproductive organs, including reduced sperm count. There were no external malformations in the offspring of male rats administered teriflunomide prior to mating with untreated female rats. Teriflunomide was embryotoxic and teratogenic in rats and rabbits at doses in the human therapeutic range. Adverse effects on the offspring were also seen when teriflunomide was administered to pregnant rats during gestation and lactation. The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low. The estimated female plasma exposure via the semen of a treated patient is expected to be 100 times lower than the plasma exposure after 14 mg of oral teriflunomide.

Juvenile toxicity

Juvenile rats receiving oral teriflunomide for 7 weeks from weaning through sexual maturity revealed no adverse effects on growth, physical or neurological development, learning and memory, locomotor activity, sexual development, or fertility. Adverse effects comprised anaemia, reduction of lymphoid responsiveness, dose-dependently diminished T cell dependent antibody response and greatly decreased IgM and IgG concentrations, which generally coincided with observations in repeat-dose toxicity studies in adult rats. However, the increase in B cells observed in juvenile rats was not observed in adult rats. The significance of this difference is unknown, but complete reversibility was demonstrated as for most of the other findings.
Due to the high sensitivity of animals to teriflunomide, juvenile rats were exposed to lower levels than those in children and adolescents at the maximum recommended human dose (MRHD).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Maize starch
Microcrystalline cellulose (E460i)
Sodium starch glycolate (Type A)
Hydroxypropylcellulose (E463)
Magnesium stearate (E470b)
Colloidal anhydrous silica

Tablet coating

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 6000 (E1521)
Talc (E553b)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

OPA/Aluminium/PVC-Aluminium blister packs of 14, 28 or 84 tablets, perforated unit dose blisters of 14 x 1, 28 x 1, 84 x 1 or 98 x 1 tablets or calendar packs of 14, 28, 84 or 98 tablets.

High Density Polyethylene (HDPE) bottles with polypropylene (PP) screw closure in packs of 84 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited
Damastown Industrial Park
Mulhuddart
Dublin 15

Dublin
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1698/001 Blister (alu/OPA/PVC/alu) 28 tablets

EU/1/22/1698/002 Blister (alu/OPA/PVC/alu) 84 tablets
EU/1/22/1698/003 Blister (alu/OPA/PVC/alu) 28 x 1 tablets (unit dose)
EU/1/22/1698/004 Blister (alu/OPA/PVC/alu) 84 x 1 tablets (unit dose)
EU/1/22/1698/005 Blister (alu/OPA/PVC/alu) 98 x 1 tablets (unit dose)
EU/1/22/1698/006 Bottle (HDPE) 84 tablets
EU/1/22/1698/007 Bottle (HDPE) 98 tablets
EU/1/22/1698/008 Blister (alu/OPA/PVC/alu) 14 tablets
EU/1/22/1698/009 Blister (alu/OPA/PVC/alu) 14 x 1 tablets (unit dose)
EU/1/22/1698/010 Blister Calendar (alu/OPA/PVC/alu) 14 tablets
EU/1/22/1698/011 Blister Calendar (alu/OPA/PVC/alu) 28 tablets
EU/1/22/1698/012 Blister Calendar (alu/OPA/PVC/alu) 84 tablets
EU/1/22/1698/013 Blister Calendar (alu/OPA/PVC/alu) 98 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 November 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) 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 RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Mylan Hungary Kft
Mylan utca 1
Komárom
H-2900
Hungary

Mylan Germany GmbH
Zweigniederlassung Bad
Homburg Benzstrasse 1
Bad Homburg v. d. Höhe
61352
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch in each Member State the MAH shall agree an educational programme with the National Competent Authority.
The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where teriflunomide is marketed, at launch and after launch, all healthcare professionals who are expected to use teriflunomide are provided with the following items:
- Summary of Product Characteristics (SmPC)
- HCP guide

- Patient Card

The HCP Guide will include the following key elements:

1. HCPs should discuss with their patients the specific safety concerns of teriflunomide detailed below including the tests and precautions needed for safe use at first prescription, and regularly during treatment as follows:
    - Risk of hepatic effects
        - Liver function tests are needed prior to the start of treatment and periodically during treatment.
        - To educate the patient about the signs and symptoms of liver disease and the need to report to their HCP if they experience any of them.
    - Potential risk of teratogenicity
        - To remind women of child-bearing potential (WOCP) including adolescents/their parents-caregivers that teriflunomide is contraindicated in pregnant women and in WOCP not using an effective contraception during and after treatment.
        - To assess regularly the potential for pregnancy in female patients including patients below 18 years old.
        - To tell female children and/or parents/caregivers of female children about the need to contact the prescribing physician once the female child under teriflunomide treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the foetus.
        - To check pregnancy status before starting treatment.
        - To educate female patients of child-bearing potential on the need for effective contraception during and after treatment with teriflunomide.
        - To remind patients to inform their doctor immediately if they stop contraception, or prior to changing contraceptive measures.
        - If female patients become pregnant despite using contraceptive measures, they should stop teriflunomide and contact their doctor immediately who should:
            - Consider and discuss with the patient the accelerated elimination procedure,
            - Report any pregnancy case to <marketing authorisation holder> by calling <local number> or visiting <URL>, irrespective of adverse outcomes observed.
    - Risk of hypertension
        - To check for a history of hypertension and that blood pressure should be appropriately managed during treatment.
        - The need for blood pressure checks before treatment and periodically during treatment.
    - Risk of haematologic effects
        - To discuss the risk of decreased blood cell counts (affecting mainly white blood cells) and the need for complete blood cell counts before treatment and periodically during treatment based on signs and symptoms.
    - Risk of infections/serious infections
        - To discuss the need to contact the doctor in the event of signs/symptoms of infection, or if the patient takes other medicines that affect the immune system. If serious infection occurs, consider the accelerated elimination procedure.
2. A reminder to provide patients/legal representative with a Patient Card, including filling-in their contact details, and to provide replacement Patient Cards as necessary.
3. A reminder to discuss the Patient Card content with the patient/legal representative regularly at each consultation at least annually during treatment.
4. To encourage patients to contact their MS physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Card.
5. At prescription renewal, adverse events are checked, ongoing risks and their prevention are discussed, and checks are made to ensure adequate monitoring is taking place.

The Patient Card is aligned with labelling information and includes the following key elements:

1. A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with teriflunomide, a medicine which:
    - Should not be used in pregnant women.
    - Requires concomitant use of effective contraception in women of child-bearing potential.
    - Requires a pregnancy status check before treatment.
    - Affects liver function.
    - Affects blood cell counts and the immune system.
2. Information to educate the patient about important side effects:
    - To pay attention to certain signs and symptoms which might indicate liver disease, or infection, and if any of these occur, to contact their doctor/HCP promptly.
    - To remind female patients to tell their doctor if breast-feeding.
    - A reminder for women of child-bearing potential including girls and their parents/ caregivers:
        - to use effective contraception during and after treatment with teriflunomide.
        - that your doctor will provide counselling on the potential risks to the foetus and on the need for effective contraception.
        - to stop treatment with teriflunomide immediately if they suspect they might be pregnant and also to contact their doctor immediately.
    - If women of child-bearing potential become pregnant:
        - To remind both patients and HCPs about the accelerated elimination procedure.
    - To remind patients to show the Patient Card to Doctors/HCPs involved with their medical care (especially in the event of medical emergencies and/or if new Doctors/HCPs are involved).
    - To record the first date of prescription and the contact details of their prescriber.
3. To encourage the patients to read the PIL thoroughly.

ANNEX III

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Teriflunomide Mylan 14 mg film-coated tablets
teriflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 14 mg of teriflunomide.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 tablets
28 tablets
84 tablets
98 tablets
14 x 1 tablets
28 x 1 tablets
84 x 1 tablets
98 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

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

Mylan Pharmaceuticals Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1698/001 Blister (alu/OPA/PVC/alu) 28 tablets
EU/1/22/1698/002 Blister (alu/OPA/PVC/alu) 84 tablets
EU/1/22/1698/003 Blister (alu/OPA/PVC/alu) 28 x 1 tablets (unit dose)
EU/1/22/1698/004 Blister (alu/OPA/PVC/alu) 84 x 1 tablets (unit dose)
EU/1/22/1698/005 Blister (alu/OPA/PVC/alu) 98 x 1 tablets (unit dose)
EU/1/22/1698/008 Blister (alu/OPA/PVC/alu) 14 tablets
EU/1/22/1698/009 Blister (alu/OPA/PVC/alu) 14 x 1 tablets (unit dose)
EU/1/22/1698/010 Blister Calendar (alu/OPA/PVC/alu) 14 tablets
EU/1/22/1698/011 Blister Calendar (alu/OPA/PVC/alu) 28 tablets
EU/1/22/1698/012 Blister Calendar (alu/OPA/PVC/alu) 84 tablets
EU/1/22/1698/013 Blister Calendar (alu/OPA/PVC/alu) 98 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Teriflunomide Mylan 14 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 AND IMMEDIATE PACKAGING

BOTTLE (WITH OR WITHOUT CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Teriflunomide Mylan 14 mg film-coated tablets
teriflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 14 mg of teriflunomide.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

84 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

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

Mylan Pharmaceuticals Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1698/006 Bottle (HDPE) 84 tablets
EU/1/22/1698/007 Bottle (HDPE) 98 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Teriflunomide Mylan

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 BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Teriflunomide Mylan 14 mg tablets
teriflunomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Oral use

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (CALENDAR PACK)

1. NAME OF THE MEDICINAL PRODUCT

Teriflunomide Mylan 14 mg tablets
teriflunomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Oral use

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PACKAGE LEAFLET

Package leaflet: Information for the patient

Teriflunomide Mylan 14 mg film-coated tablets
teriflunomide

Read all of this leaflet carefully before you start taking 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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Teriflunomide Mylan is and what it is used for
2. What you need to know before you take Teriflunomide Mylan
3. How to take Teriflunomide Mylan
4. Possible side effects
5. How to store Teriflunomide Mylan
6. Contents of the pack and other information

1. What Teriflunomide Mylan is and what it is used for

What Teriflunomide Mylan is
Teriflunomide Mylan contains the active substance teriflunomide which is an immunomodulatory agent and adjusts the immune system to limit its attack on the nervous system.

What Teriflunomide Mylan is used for
Teriflunomide is used in adults and in children and adolescents (10 years of age and older) to treat relapsing remitting multiple sclerosis (MS).

What multiple sclerosis is
MS is a long-term illness that affects the central nervous system (CNS). The CNS is made up of the brain and spinal cord. In multiple sclerosis, inflammation destroys the protective sheath (called myelin) around the nerves in the CNS. This loss of myelin is called demyelination. This stops nerves from working properly.

People with relapsing form of multiple sclerosis will have repeated attacks (relapses) of physical symptoms caused by their nerves not working properly. These symptoms vary from patient to patient but usually involve:
- difficulty walking
- vision problems
- balance problems.

Symptoms may disappear completely after the relapse is over, but over time, some problems may remain between relapses. This can cause physical disabilities that may interfere with your daily activities.

How Teriflunomide Mylan works
Teriflunomide Mylan helps to protect against attacks on the central nervous system by the immune system by limiting the increase of some white blood cells (lymphocytes). This limits the inflammation that leads to nerve damage in MS.

2. What you need to know before you take Teriflunomide Mylan

Do not take Teriflunomide Mylan:
- if you are allergic to teriflunomide or any of the other ingredients of this medicine (listed in section 6)
- if you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking teriflunomide or leflunomide
- if you have severe liver problems
- if you are pregnant, think you may be pregnant, or are breast-feeding
- if you suffer from a serious problem which affects your immune system e.g. acquired immunodeficiency syndrome (AIDS)
- if you have a serious problem with your bone marrow, or if you have low numbers of red or white cells in your blood or a reduced number of blood platelets
- if you are suffering from a serious infection
- if you have severe kidney problems which require dialysis
- if you have very low levels of proteins in your blood (hypoproteinaemia).

If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor or pharmacist before taking Teriflunomide Mylan if:
- you have liver problems, and/or if you drink large amounts of alcohol. Your doctor will carry out blood tests before and during treatment to check how well your liver is working. If your test results show a problem with your liver, your doctor may stop your treatment with Teriflunomide Mylan. Please read section 4.
- you have high blood pressure (hypertension) whether it is controlled with medicines or not. Teriflunomide Mylan can cause an increase in blood pressure. Your doctor will check your blood pressure before the start of treatment and regularly thereafter. Please read section 4.
- you have an infection. Before you take Teriflunomide Mylan, your doctor will make sure you have enough white blood cells and platelets in your blood. As Teriflunomide Mylan decreases the number of white cells in the blood this may affect your ability to fight the infection. Your doctor may do blood tests to check your white blood cells if you think you have any infection. Herpes virus infections, including oral herpes or herpes zoster (shingles) may occur with teriflunomide treatment. In some cases, serious complications have occurred. You should inform your doctor immediately if you suspect you have any symptoms of herpes virus infection. Please read section 4.
- you have severe skin reactions
- you have respiratory symptoms
- you have weakness, numbness and pain in the hands and feet
- you are going to have a vaccination
- you take leflunomide with Teriflunomide Mylan
- you are switching to or from Teriflunomide Mylan
- you are due to have a specific blood test (calcium level). Falsely low levels of calcium can be detected.

Respiratory reactions
Tell your doctor if you have unexplained cough and dyspnoea (shortness of breath). Your doctor may perform additional tests.

Children and adolescents
Teriflunomide Mylan is not intended for use in children under 10 years of age, as it has not been studied in MS patients in this age group.
The warnings and precautions listed above also apply to children. The following information is important for children and their caregivers:
- inflammation of the pancreas has been observed in patients receiving teriflunomide. Your child’s doctor may carry out blood tests if an inflammation to the pancreas is suspected.

Other medicines and Teriflunomide Mylan
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.
In particular, tell your doctor or pharmacist if you are taking any of the following:
- leflunomide, methotrexate and other medicines that affect the immune system (often called immunosuppressants or immunomodulators)
- rifampicin (a medicine used to treat tuberculosis and other infections)
- carbamazepine, phenobarbital, phenytoin for epilepsy
- St John's wort (a herbal medicine for depression)
- repaglinide, pioglitazone, nateglinide, or rosiglitazone for diabetes
- daunorubicin, doxorubicin, paclitaxel, or topotecan for cancer
- duloxetine for depression, urinary incontinence or in kidney disease in diabetics
- alosetron for the management of severe diarrhoea
- theophylline for asthma
- tizanidine, a muscle relaxant
- warfarin, an anticoagulant used to make the blood thinner (i.e. more fluid) in order to avoid blood clots
- oral contraceptives (containing ethinylestradiol and levonorgestrel)
- cefaclor, benzylpenicillin (penicillin G), ciprofloxacin for infections
- indometacin, ketoprofen for pain or inflammation
- furosemide for heart disease
- cimetidine for reducing gastric acid
- zidovudine for HIV infection
- rosuvastatin, simvastatin, atorvastatin, pravastatin for hypercholesterolemia (high cholesterol)
- sulfasalazine for inflammatory bowel disease or rheumatoid arthritis
- cholestyramine for high cholesterol or relief from itching in liver disease
- activated charcoal to reduce absorption of medicines or other substances.

Pregnancy and breast-feeding
Do not take Teriflunomide Mylan if you are, or think you may be **pregnant**. If you are pregnant or become pregnant while taking Teriflunomide Mylan the risk of having a baby with birth defects is increased. Women of childbearing potential must not take this medicine without using reliable contraceptive measures.
If your child/adolescent daughter reaches menses while taking teriflunomide, you should inform the doctor, who will provide specialist counselling regarding contraception and the potential risks in case of pregnancy.

Tell your doctor if you plan to become pregnant after stopping treatment with Teriflunomide Mylan as you need to ensure that most of this medicine has left your body before trying to become pregnant. The elimination of the active substance may take up to 2 years to occur naturally. The time can be reduced to a few weeks by taking certain medicines which speed up removal of Teriflunomide Mylan from your body.
In either case it should be confirmed by a blood test that the active substance has been sufficiently removed from your body and you need confirmation from your treating physician that the blood level of Teriflunomide Mylan is low enough to allow you to become pregnant.

For further information on the laboratory testing please contact your doctor.

If you suspect that you are pregnant while taking Teriflunomide Mylan or in the two years after you have stopped treatment, you must discontinue Teriflunomide Mylan and contact your doctor **immediately** for a pregnancy test. If the test confirms that you are pregnant, your doctor may suggest treatment with certain medicines to remove Teriflunomide Mylan rapidly and sufficiently from your body, as this may decrease the risk to your baby.

<u>Contraception</u>

You must use an effective method of contraception during and after treatment with Teriflunomide Mylan.
Teriflunomide remains in your blood for a long time after you stop taking it. Continue to use effective contraception after you stop treatment.

- Do this until the levels of Teriflunomide Mylan in your blood are low enough - your doctor will check this.
- Talk with your doctor about the best method of contraception for you and any potential need for contraception change.

Do not take Teriflunomide Mylan when you are breast-feeding, as teriflunomide passes into the breast milk.

Driving and using machines
Teriflunomide Mylan might make you feel dizzy which may impair your ability to concentrate and react. If you are affected, do not drive or use machines.

Teriflunomide Mylan contains lactose
Teriflunomide Mylan contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Teriflunomide Mylan contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Teriflunomide Mylan

Treatment with Teriflunomide Mylan will be overseen by a doctor who is experienced in the treatment of multiple sclerosis.

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Adults
The recommended dose is one 14 mg teriflunomide tablet daily.

Children and adolescents (10 years of age and above)
The dose depends on body weight:
- Children with body weight greater than 40 kg: one 14 mg tablet daily.
- Children with body weight less than or equal to 40 kg: one 7 mg tablet daily.

Teriflunomide 7 mg strength is not marketed by Mylan Pharmaceuticals Limited but may be available from other Marketing Authorisation Holders.

Children and adolescents who reach a stable body weight above 40 kg will be instructed by their doctor to switch to one 14 mg tablet daily.

Route/method of administration
Teriflunomide Mylan is for oral use. Teriflunomide Mylan is taken every day as a single dose at any time of the day.
You should swallow the tablet whole with some water.
Teriflunomide Mylan may be taken with or without food.

If you take more Teriflunomide Mylan than you should
If you have taken too much Teriflunomide Mylan, call your doctor straight away. You may experience side effects similar to those described in section 4 below.

If you forget to take Teriflunomide Mylan
Do not take a double dose to make up for a forgotten tablet. Take your next dose at the scheduled time.

If you stop taking Teriflunomide Mylan
Do not stop taking Teriflunomide Mylan or change your dose without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may happen with this medicine.

Serious side effects

Some side effects could be or could become serious, if you experience any of these, **tell your doctor immediately:**

Common (may affect up to 1 in 10 people)
- Inflammation of the pancreas which might include symptoms of pain in the abdominal area, nausea, or vomiting (the frequency is common in paediatric patients and uncommon in adult patients).

Uncommon (may affect up to 1 in 100 people)
- Allergic reactions which might include symptoms of rash, hives, swelling of lips, tongue or face or sudden difficulty breathing.
- Severe skin reactions which might include symptoms of skin rash, blistering, fever or ulcers in your mouth.
- Severe infections or sepsis (a potentially life-threatening type of infection) which might include symptoms of high fever, shaking, chills, reduced urine flow, or confusion.
- Inflammation of the lungs which might include symptoms of shortness of breath or persistent cough.

Not known (frequency cannot be estimated from the available data)
- Serious liver disease which might include symptoms of yellowing of your skin or the whites of your eyes, darker urine than normal, unexplained nausea and vomiting, or abdominal pain.

Other side effects can occur with the following frequencies:

Very common (may affect more than 1 in 10 people)
- Headache
- Diarrhoea, feeling sick
- Increase in ALT (increase in blood levels of certain hepatic enzymes) shown in tests
- Hair thinning.

Common (may affect up to 1 in 10 people)
- Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, sore throat and discomfort when swallowing, cystitis, gastroenteritis viral, tooth infection, laryngitis, fungal infection of the foot
- Herpes virus infections, including oral herpes and herpes zoster (shingles) with symptoms such as blisters, burning, itching, numbness or pain of the skin, typically on one side of the upper body or face, and other symptoms, like fever and weakness

- Laboratory values: a decrease in the number of red blood cells (anaemia), changes in liver and white blood cell test results (see section 2), as well as elevations in a muscle enzyme (creatine phosphokinase) have been observed
- Mild allergic reactions
- Feeling anxious
- Pins and needles, feeling weak, numb, tingling or pain in the lower back or leg (sciatica); feeling numb, burning, tingling or pain in the hands and fingers (carpal tunnel syndrome)
- Feeling your heartbeat
- Increase in blood pressure
- Being sick (vomiting), toothache, upper abdominal pain
- Rash, acne
- Pain of the tendons, joints, bones, muscle pain (musculoskeletal pain)
- Needing to urinate more often than usual
- Heavy periods
- Pain
- Lack of energy or feeling weak (asthenia)
- Weight loss.

Uncommon (may affect up to 1 in 100 people)
- Decrease in the number of blood platelets (mild thrombocytopenia)
- Increased feeling or sensitivity, especially in the skin; stabbing or throbbing pain along one or more nerves, problems in the nerves of the arms or legs (peripheral neuropathy)
- Nail disorders, severe skin reactions
- Post-traumatic pain
- Psoriasis
- Inflammation of mouth/lips
- Abnormal levels of fats (lipids) in the blood
- Inflammation of the colon (colitis).

Rare (may affect up to 1 in 1,000 people)
- Inflammation or injury of the liver.

Not known (frequency cannot be estimated from the available data)
- Respiratory hypertension.

Children (10 years of age and above) and adolescents
The side effects listed above also apply to children and adolescents. The following additional information is important for children, adolescents, and their caregivers:

Common (may affect up to 1 in 10 people)
- Inflammation of the pancreas.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Teriflunomide Mylan

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after ‘EXP’. The expiry date refers to the last day of that month.

Store below 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Teriflunomide Mylan contains
- The active substance is teriflunomide. Each tablet contains 14 mg of teriflunomide.
- The other ingredients are:
  Tablet core: lactose monohydrate , maize starch, microcrystalline cellulose (E460i), sodium starch glycolate (Type A) , hydroxypropylcellulose (E463), magnesium stearate (E470b), colloidal anhydrous silica;
  Tablet coat: hypromellose (E464), titanium dioxide (E171), talc (E553b), macrogol 6000 (E1521), indigo carmine aluminium lake (E132).

What Teriflunomide Mylan looks like and contents of the pack
Pale blue to pastel blue, round, biconvex (surface curved outwards on both sides) with 'T' on one side and '1' on the other side, approximately 7.6 mm diameter.

Teriflunomide Mylan is available in blister packs of 14, 28 or 84 tablets, perforated unit dose blisters of 14 x 1, 28 x 1, 84 x1 or 98 x 1 tablets, calendar packs of 14, 28, 84 or 98 tablets and in bottles containing 84 or 98 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Mylan Pharmaceuticals Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Ireland

Manufacturer
Mylan Hungary Kft
Mylan utca 1
Komárom
H-2900
Hungary

Mylan Germany GmbH
Zweigniederlassung Bad
Homburg Benzstrasse 1
Bad Homburg v. d. Höhe
61352
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Viatris
Tél/Tel: + 32 (0)2 658 61 00

България
Майлан ЕООД
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Lietuva
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Luxembourg/Luxemburg
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Mylan BV
Tel: +31 (0)20 426 3300

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Österreich
Arcana Arzneimittel GmbH
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Mylan Healthcare Sp. z o.o.
Tel: + 48 22 546 64 00

Portugal
Mylan, Lda.
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România
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Slovenija
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Slovenská republika
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Suomi/Finland
Viatris Oy
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Viatris AB
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United Kingdom (Northern Ireland)
Mylan IRE Healthcare Limited
Tel: +353 18711600

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for teriflunomide, the scientific conclusions of PRAC are as follows:

In view of available data on herpes virus infections from clinical trial(s), the literature and spontaneous reports, including in some cases a plausible temporal relationship, a positive de-challenge and/or re-challenge, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between teriflunomide and herpes virus infections is at least a reasonable possibility. The PRAC concluded that the product information of products containing teriflunomide should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for teriflunomide the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing teriflunomide is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.