Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Teriflunomide Clonmel Healthcare 7 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 7 mg of teriflunomide.

Excipient with known effect
Each tablet contains 45 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Green to pale green coloured, round, film-coated tablet diameter plain on both sides, diameter 6 mm, thickness 3 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Teriflunomide Clonmel Healthcare 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.

Film-coated tablets can be taken with or without food.

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 than10 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.

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, leukopenia, 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 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 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, leukopenia, 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.

Skin ulcers and impaired wound healing may potentially occur in patients during therapy with teriflunomide. If teriflunomide-associated skin ulcer is suspected, if skin ulcers persist despite appropriate therapy, or if there is a high risk for impaired wound healing after surgery, consider teriflunomide discontinuation and an accelerated drug elimination procedure. The decision to resume teriflunomide should be based on clinical judgment of adequate wound healing.

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 immuno modulating 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 Clonmel Healthcare

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

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 dose, 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 *invivo*. 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 teriflunomideon 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 coadministration 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 in adult patients, 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	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		Mild allergic	Hyper-sensitivity reactions		

disorders		reactions.	(immediate or delayed) including anaphylaxis and angioedema.		
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).
Metabolism and nutrition disorders			Dyslipidaemia.		
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 administration site conditions		Pain, asthenia[a].			
Investigations		Weight decrease, neutrophil count decrease[b], white blood cell count decrease[b], blood creatine phosphokinase increased.			
Injury, poisoning and procedural			Post-traumatic pain.		

complications					

[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 teriflunomide 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=1 002)**
> 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 mmHg in 19.9 % of patients receiving 14 mg/day teriflunomide as compared to 15.5 % receiving placebo
- systolic blood pressure was > 160 mmHg in 3.8 % of patients receiving 14 mg/day teriflunomide as compared to 2.0 % receiving placebo
- diastolic blood pressure was > 90 mmHg 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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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, Dihydroorotate dehydrogenase (DHODH) inhibitors
ATC Code: L04AK02

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 to17 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 ($CI_{95\%}$) of confirmed relapse at week 96 *Probability ($CI_{95\%}$) 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 ($CI_{95\%}$)	0.66 (0.39, 1.11) ^	
Time to first confirmed clinical relapse or high MRI activity, Probability ($CI_{95\%}$) of confirmed relapse or high MRI activity at week 96 *Probability ($CI_{95\%}$) 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 ($CI_{95\%}$)	0.57 (0.37, 0.87)*	
Key MRI endpoints		
Adjusted number of new or enlarged T2 lesions, Estimate ($CI_{95\%}$) *Estimate ($CI_{95\%}$), 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 ($CI_{95\%}$) *Relative risk ($CI_{95\%}$), 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 ($CI_{95\%}$)	1.90 (0.66, 5.49)	7.51 (2.48, 22.70)
Relative risk ($CI_{95\%}$)	0.25 (0.13, 0.51)***	
^ $p \geq 0.05$ 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 sulphate 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 inspecific 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 (≤ 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 leukopenia, 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
Cellulose microcrystalline
Sodium starch glycolate (Type A)
Hydroxypropylcellulose (E 463)
Maize starch
Silica, colloidal anhydrous
Magnesium stearate

Tablet coating
Hypromellose (E464)
Lactose monohydrate
Calcium carbonate (E170)
Triacetin (E 1518)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

'oPA/Alu/PVC with an aluminium foil blister or perforated unit-dose blister packed in cartons.

Each pack contains 14, 28, 84 or 98 film-coated tablets or 14x1, 28x1, 84x1 or 98x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/401/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd October 2026

10 DATE OF REVISION OF THE TEXT