

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

TERIGIO 14 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Active substance:

Teriflunomide 14 mg

Excipients with known effect:

Lactose monohydrate (from cow's milk) 74.5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale blue to pastel blue, biconvex, round film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TERIGIO is indicated for the treatment of adult patients and pediatric patients with a body weight > 40 kg and 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.

Pediatric population (10 years and older)

In pediatric patients (10 years of age and above), the recommended dose is dependent on body weight:

- Pediatric patients with body weight > 40 kg: 14 mg once daily.
- Pediatric patients with body weight ≤ 40 kg: 7 mg once daily.

Pediatric 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.

Method of administration

The film-coated tablets are for oral use. The tablets should be swallowed whole with some water.

Additional information on special populations

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).

Pediatric 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.

Elderly population

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

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 anemia, 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 hypoproteinemia, 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, together 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 normalization of transaminase levels.

Hypoproteinemia

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 hypoproteinemia, e.g. in nephrotic syndrome. Teriflunomide should not be used in patients with conditions of severe hypoproteinemia.

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). However, based on the immunomodulatory effect of teriflunomide, if a patient develops a serious infection, suspending treatment with TERIGIO 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 TERIGIO should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with TERIGIO 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 dyspnea, 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.

Hematological 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 anemia, 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 hematological 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 hematological reactions, including pancytopenia, TERIGIO and any concomitant myelo-suppressive 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 generalized 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 TERIGIO develops a confirmed peripheral neuropathy, discontinuing TERIGIO 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 TERIGIO

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 TERIGIO was immediately started. Therefore, caution is required when switching patients from natalizumab to TERIGIO.

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

Interference with determination of ionized calcium levels

The measurement of ionized calcium levels might show falsely decreased values under treatment with leflunomide and/or teriflunomide (the active metabolite of leflunomide) depending on the type of ionized calcium analyzer used (e.g. blood gas analyzer). Therefore, the plausibility of observed decreased ionized 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.

Pediatric population

Pancreatitis

In the pediatric 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).

Lactose

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

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 metabolized 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 metabolized 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 normalized ratio (INR) was observed when teriflunomide was coadministered 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 coadministered 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-CoA 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.

Additional information on special populations

No interaction studies have been conducted.

Pediatric population

No interaction studies have been conducted.

4.6. Pregnancy and lactation

General advice

Pregnancy category is “X”.

Women with childbearing potential / Contraception

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 TERIGIO treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the fetus. Referral to a gynecologist 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 fetus.

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 fetus is to be expected.

For further information on the sample testing please contact the Marketing Authorization 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 fertilization is required.

Both cholestyramine and activated powdered charcoal may influence the absorption of estrogens 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.

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).

Use in males

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

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

TERIGIO 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%), diarrhea (13.1%, 13.6%), increased ALT (13%, 15%), nausea (8%, 10.7%), and alopecia (9.8%, 13.5%). In general, headache, diarrhea, 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 ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ 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.

Infections and infestations

Common : Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis
Uncommon : Severe infections including sepsis^a

Blood and lymphatic system disorders

Common : Neutropenia^b, anemia
Uncommon : Mild thrombocytopenia (platelets $<100\text{G/l}$)

Immune system disorders

Common : Mild allergic reactions
Uncommon : Hypersensitivity reactions (immediate or delayed) including anaphylaxis and angioedema

Psychiatric disorders

Common : Anxiety

Nervous system disorders

Very common : Headache
Common : Paresthesia, sciatica, carpal tunnel syndrome
Uncommon : Hyperesthesia, neuralgia, peripheral neuropathy

Cardiac disorders

Common : Palpitations

Vascular disorders

Common : Hypertension^b

Respiratory, thoracic and mediastinal disorders

Uncommon : Interstitial lung disease
Unknown : Pulmonary hypertension

Gastrointestinal disorders

Very common : Diarrhea, nausea
Common : Pancreatitis^{b,c}, abdominal pain upper, vomiting, toothache
Uncommon : Stomatitis, colitis

Hepatobiliary disorders

Very common : Alanine aminotransferase (ALT) increase^b
Common : Gamma-glutamyltransferase (GGT) increase^b, aspartate aminotransferase increase^b
Rare : Acute hepatitis
Unknown : Drug-induced liver injury (DILI)

Metabolism and nutrition disorders

Uncommon : Dyslipidemia

Skin and subcutaneous tissue disorders

Very common : Alopecia
Common : Rash, acne
Uncommon : Nail disorders, psoriasis (including pustular)^{a,b}, severe skin reactions^a

Musculoskeletal, connective tissue and bone disorders

Common : Musculoskeletal pain, myalgia, arthralgia

Renal and urinary disorders

Common : Pollakiuria

Reproductive system and breast disorders

Common : Menorrhagia

General disorders and administration site conditions

Common : Pain, asthenia^a

Laboratory investigations

Common : Weight decrease, neutrophil count decrease^b, white blood cell count decrease^b, blood creatine phosphokinase increase

Injury, poisoning and procedural complications

Uncommon : 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 pediatrics; 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 generalized 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=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.

Hematological 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 stabilized 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 mono-neuropathy (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 necrotizing pancreatitis and pancreatic pseudo-cyst. Pancreatic events may occur at any time during treatment with teriflunomide, which may lead to hospitalization and/or require corrective treatment.

Pediatric population

The observed safety profile in pediatric patients (from 10 to 17 years-old) receiving teriflunomide daily was overall similar to that seen in adult patients. However, in the pediatric 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 hospitalization and required corrective treatment. In pediatric 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 non-serious 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 hospitalization. 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 pediatric 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.
- Creatinine phosphokinase (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 authorization 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.

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 reduction in lymphocyte count, of less than $0.3 \times 10^9/l$, 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	0.5
<i>Risk difference (CI_{95%})</i>	-0.17 (-0.26, -0.08)***		-0.18 (-0.27, -0.09)****	
Relapse-free <i>week</i> <i>108</i>	56.5%	45.6%	57.1%	46.8%
Hazard ratio (CI _{95%})	0.72, (0.58, 0.89)**		0.63, (0.5, 0.79)****	
3-month Sustained Disability Progression <i>week</i> <i>108</i>	20.2%	27.3%	15.8%	19.7%
<i>Hazard ratio (CI_{95%})</i>	0.7 (0.51, 0.97)*		0.68 (0.47, 1.00)*	
6-month Sustained Disability Progression <i>week</i> <i>108</i>	13.8%	18.7%	11.7%	11.9%
<i>Hazard ratio (CI_{95%})</i>	0.75 (0.5, 1.11)		0.84 (0.53, 1.33)	
MRI endpoints				
Change in BOD <i>week 108(1)</i>	0.72	2.21	Not measured	
<i>Change relative to placebo</i>	67% **			
Mean Number of Gd-enhancing lesions at week 108	0,38	1.18		

<i>Change relative to placebo (CI_{95%})</i>	-0.8 (-1.2, -0.39)****	
Number of unique active lesions /scan	0.75	2.46
<i>Change relative to placebo (CI_{95%})</i>	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).

Pediatric population

Children and adolescents (10 to 17 years of age)

Study EFC11759/TERIKIDS was an international double-blind, placebo-controlled study in pediatric 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 magnetic resonance imaginf (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)	Teriflunomide (N=57)
Clinical endpoints		
Time to first confirmed clinical relapse, Probability (95%CI) of confirmed relapse at Week 96	0.39 (0.29, 0.48)	0.53 (0.36, 0.68)
Probability (95%CI) of confirmed relapse at Week 48	0.3 (0.21, 0.39)	0.39 (0.3, 0.52)
Hazard ratio (CI _{95%})	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	0.51 (0.41, 0.6)	0.72 (0.58, 0.82)
Probability (95%CI) of confirmed relapse		0.56 (0.42, 0.68)

<i>or high MRI activity at Week 48</i>	<i>0.38 (0.29, 0.47)</i>	
Key MRI endpoints		
Adjusted number of new or enlarged T2 lesions, Estimate (95% CI) <i>Estimate (95% CI), post-hoc analysis also adjusted for baseline T2 counts</i>	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), <i>post-hoc analysis also adjusted for baseline T2 counts</i>	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 teriflunomide in children from birth to less than 10 years in treatment of multiple sclerosis (see section 4.2 for information on pediatric 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 metabolized 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 medicinal 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 feces (37.5%) and urine (22.6%). After the rapid elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in feces). 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.

Pediatric population

In pediatric 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 pediatric 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/ gastro intestinal tract, reproductive organs, and pancreas. Evidence of an oxidative effect on red blood cells was also observed. Anemia, 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-fetal 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 anemia, 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

Lactose monohydrate (from cow's milk)
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Sodium starch glycolate (Type A)
Colloidal silicon dioxide
Magnesium stearate
Opadry 03K205008 Blue

Opadry 03K205008 Blue
Hydroxypropyl methyl cellulose
Triacetin
Titanium dioxide
Indigo carmine (Blue-2) Al-lake

6.2. Incompatibilities

There is not enough data.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at room temperature below 30°C.

6.5. Nature and contents of container

Blisters consisting of PA/ALU/PVC foil and aluminum foil are used as the primary packaging material of this medicinal product. The blisters are packed in a cardboard box. Each cardboard box includes 2 blisters containing a total of 28 tablets (14 tablets in each blister).

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

SABA İlaç San. Ve Tic. A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2022/229

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization : 20.04.2022
Renewal of authorization :



10. DATE OF REVISION OF THE TEXT