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TENEX

Teriflunomide Film Coated Tablets 14 mg

1. Product Name

Teriflunomide Film Coated Tablets 14 mg

2. Name and Strength of Active Substance(s)

Each Film coated tablet contains Teriflunomide 14 mg

3. Product Description

Tenex -Teriflunomide Film Coated Tablets 14 mg is Pale blue to pastel blue coloured, pentagonal film coated tablet, debossed with S28 on one side and plain on the other side.

4. Pharmacodynamics

Pharmacotherapeutic group: 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), required for the de novo pyrimidine synthesis. As a consequence teriflunomide reduces the proliferation of dividing cells that need 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 109/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.

Paediatric population

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 Recommended Dose on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Teriflunomide in one or more subsets of the paediatric population in multiple sclerosis (see section Recommended Dose on paediatric use).

5. Pharmacokinetics

Absorption

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

Food does not have a clinically relevant effect on teriflunomide pharmacokinetics. From the mean predicted pharmacokinetic parameters calculated from the population pharmacokinetic (PopPK) analysis using data from healthy volunteers and MS patients, there is a slow approach to steady-state concentration (i.e., approximately 100 days (3.5 months) to attain 95% of steady-state concentrations) and the estimated AUC accumulation ratio is approximately 34-fold.

Distribution

Teriflunomide is extensively bound to plasma protein (>99%), probably albumin and is mainly distributed in plasma. The volume of distribution is 11 l after a single intravenous (IV) administration. However, this is most likely an underestimation since extensive organ distribution was observed in rats.

Biotransformation

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

Elimination

Teriflunomide is excreted in the gastrointestinal tract mainly through the bile as unchanged medicinal product 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 t1/2z 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, Elderly, Paediatric patients

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.

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.

6. Indication

Teriflunomide tablets is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

7. Recommended dose

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

Posology

The recommended dose of teriflunomide is 14 mg once daily.

Special populations

Elderly population

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

Renal impairment

No dosage 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

Hepatic impairment

No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. Teriflunomide is contraindicated in patients with severe hepatic impairment.

Paediatric population

The safety and efficacy of teriflunomide in children aged from 10 to less than 18 years has not yet been established. There is no relevant use of teriflunomide in children aged from birth to less than 10 years for the treatment of multiple sclerosis.

No data are available.

Method of administration

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

8. Route of administration

Oral route

9. Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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 Pregnancy must be excluded before start of treatment.

Breast-feeding women.

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

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

Patients with severe active infection until resolution

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.

10. Warning and precautions

Monitoring

Before treatment

- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell count including differential white blood cell and platelet count.

During treatment

- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell counts should be performed based on 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.

Hepatic effects

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

Liver enzymes should be assessed before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly.

Teriflunomide therapy should be discontinued if liver injury is suspected; consider discontinuing teriflunomide therapy if elevated liver enzymes (greater than 3-fold ULN) are confirmed. Patients with preexisting liver disease may be at increased risk of developing elevated liver enzymes when taking teriflunomide and should be closely monitored for signals of liver disease.

The medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

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. 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. However, based on the immunomodulatory effect of teriflunomide, if a patient develops a serious infection, suspending treatment with Teriflunomide Tablets 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 Tablets should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with Teriflunomide Tablets 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. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with Teriflunomide Tablets.

Respiratory reactions

No cases of interstitial lung diseases (ILD) have been reported with teriflunomide in the clinical trials. However, ILD, which is a potentially fatal disorder, has been reported during treatment with leflunomide, the parent compound. ILD may occur acutely during therapy; the risk is increased in patients who had a history of ILD when treated with leflunomide.

Pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate.

Haematological effects

A mean decrease less than 15% from baseline affecting white blood cell count has been observed 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 with Teriflunomide Tablets and the complete blood cell count should be assessed during Teriflunomide Tablets therapy as indicated by clinical signs and symptoms (e.g., infections).

In patients with pre-existing anaemia, leucopenia, and /or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of haematological disorders is increased. If such effects occur, the accelerated elimination procedure to reduce plasma levels of teriflunomide should be considered.

In cases of severe haematological reactions, including pancytopenia, Teriflunomide Tablets and any concomitant myelosuppressive treatment must be discontinued and a teriflunomide accelerated elimination procedure should be considered.

Skin reactions

Cases of severe skin reactions have been reported post-marketing (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

In patients treated with leflunomide, the parent compound, very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported.

In case of ulcerative stomatitis, teriflunomide administration should be discontinued. If skin and/or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome), 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.

Peripheral neuropathy

Cases of peripheral neuropathy have been reported in patients receiving Teriflunomide Tablets most patients improved after discontinuation of Teriflunomide Tablets. 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 Tablets develops a confirmed peripheral neuropathy, consider discontinuing Teriflunomide Tablets therapy and performing the accelerated elimination procedure.

Vaccination

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

Immunosuppressive or immunomodulating therapies

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

Switching to or from Teriflunomide Tablets

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

Based on the half-life of fingolimod, a 6-week interval without therapy is needed for clearance from the circulation and a 1 to 2month period is needed for lymphocytes to return to normal range following discontinuation of fingolimod. Starting Teriflunomide Tablets 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 t1/2z was approximately 19 days after repeated doses of 14 mg. If a decision is made to stop treatment with Teriflunomide Tablets, 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 Tablets. This may lead to an additive effect on the immune system and caution is, therefore, indicated.

Lactose

Since Teriflunomide Tablets contain lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

11. 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 Cmax 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 Cmax and AUC0-24 (1.58- and 1.54-fold, respectively) and levonorgestrel Cmax and AUC0-24 (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 Cmax and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 in vivo. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetin, 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

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

Effect of teriflunomide on organic anion transporter 3 (OAT3) substrates

There was an increase in mean cefaclor Cmax 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 Cmax 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.

12. Fertility, Pregnancy and Lactation

Use in males

The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low.

Pregnancy

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

Teriflunomide may cause serious birth defects when administered during pregnancy. Teriflunomide is contraindicated in pregnancy.

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.

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must 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.

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.

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.

Fertility

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

13. Side Effect

Tabulated list of adverse reactions

Adverse reactions reported with Teriflunomide Tablets in placebo-controlled studies, reported for teriflunomide 7 mg or 14 mg at ≥ 1% higher rate than for placebo, are shown below. Frequencies were defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Influenza, Upper respiratory tract infection, Urinary tract infection, Bronchitis, Sinusitis, Pharyngitis, Cystitis, Gastroenteritis viral, Oral herpes, Tooth infection, Laryngitis, Tinea pedis				Severe infections including sepsis [a]
Blood and lymphatic system disorders		Neutropenia Anaemia	Mild thrombocytopenia (platelets <100G/l)			
Immune system disorders		Mild allergic reactions				Hypersensitivity 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				
Respiratory, thoracic and mediastinal disorders					Interstitial lung disease*	
Gastrointestinal disorders	Diarrhoea, Nausea	Abdominal pain upper, Vomiting, Toothache				Pancreatitis, Stomatitis
Skin and subcutaneous tissue disorders	Alopecia	Rash, Acne				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				
Investigations	Alanine aminotransferase (ALT) increase	Gamma- glutamyl transferase (GGT) increase, Aspartate aminotransferase increase, Weight decrease, Neutrophil count decrease, White blood cell count decrease, Blood creatine phosphokinase increased				
Injury, poisoning and procedural complications			Post-traumatic pain			

*: Based on leflunomide data only

Description of selected adverse reactions

Alopecia

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

Hepatic effects

During placebo-controlled studies 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 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, 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 postmarketing.

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 AUBAGIO, 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, 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 the 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 warnings and precautions for use).

Asthenia

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

Reporting of suspected adverse reactions

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

14. 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.

15. Effect on ability to drive and use machine

Teriflunomide Tablets 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.

16. Preclinical safety data

Not applicable for generic products.

17. Pharmaceutical particulars

17.1 List of excipients

- Lactose Monohydrate
- Microcrystalline Cellulose
- Hydroxypropyl Cellulose
- Sodium Starch Glycolate
- Colloidal Silicon Dioxide
- Magnesium Stearate
- Opadry Blue 03B505062
- Purified water

17.2 Incompatibilities

Not applicable.

17.3 Shelf life

2 years

17.4 Special precautions for storage

Store below 30°C.

Protect from light and moisture.

17.5 Nature and contents of container

Alu-Alu blister pack containing tablets placed in a printed carton along with pack Insert.

Pack size: 2 X 14 tablets

17.6 Special precautions for disposal and other handling

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

18. Name and Address of The Manufacturer

Shilpa Medicare Limited
Unit IV, Plot S-20 to S-26, Pharma SEZ, TSIIC,
Green Industrial Park, Polepally (V),
Jadcherla (Md), Mahabubnagar (Dt.),
Telangana, 509301, INDIA.

19. Name & Address of Product Registration Holder (PRH):

Unimed Sdn Bhd
53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara 52200,
Kuala Lumpur, Malaysia.

20. Date of Revision of Package Insert

26.06.2025

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