SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AUBAMIDE (14 mg film-coated tablets)

WARNING: HEPATOTOXICITY and RISK OF TERATOGENICITY
Hepatotoxicity:
Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for AUBAMIDE because recommended doses of AUBAMIDE and leflunomide result in a similar range of plasma concentrations of AUBAMIDE. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAMIDE and monitor alanine aminotransferase (ALT) levels at least monthly for six months. If AUBAMIDE-induced liver injury is suspected , discontinue AUBAMIDE and start accelerated elimination procedure.
Risk of teratogenicity:
Based on animal data, AUBAMIDE may cause major birth defects if used during pregnancy. AUBAMIDE is contra-indicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during AUBAMIDE treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 14 mg of teriflunomide.

Contains sugar:

Each AUBAMIDE 14 mg film-coated tablet contains 76 mg of sugar (lactose monohydrate).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablets

Light yellow, round shaped, biconvex film coated tablets, debossed with “A” on one side and “14” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUBAMIDE is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of relapses and delay the accumulation of physical disability in adult patients. (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 medical practitioner experienced in managing multiple sclerosis.

The recommended dose of AUBAMIDE is 14 mg orally once daily.

AUBAMIDE can be taken with or without food.

Special populations

Elderly population

AUBAMIDE has not been specifically studied in the elderly.

Renal impairment

No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment.

Hepatic impairment

No dosage adjustment is necessary for patients with mild and moderate hepatic impairment.

Teriflunomide is contraindicated in patients with severe hepatic impairment (see **section 4.3**).

Paediatric population

The safety and efficacy of AUBAMIDE in children aged 0 to 18 years have not yet been established. Use in this age group is not recommended.

4.3 Contraindications

Hypersensitivity to teriflunomide, leflunomide or to any of the excipients listed in **section 6.1**.

Patients with severe hepatic impairment

Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with AUBAMIDE and thereafter as long as its plasma levels are above 0,02 mg/L . Pregnancy must be excluded before start of treatment (see **section 4.6**).

Breast-feeding women (see **section 4.6**).

Leflunomide is the parent compound of teriflunomide, co-administration of AUBAMIDE with leflunomide is contraindicated.

Patients with severe immunodeficiency states, e.g. bone marrow disease, or severe uncontrolled infection.

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

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

No evaluations were done on patients with severe renal impairment undergoing dialysis as there is insufficient clinical data available for this patient group.

Patients with severe hypoproteinaemia.

4.4 Special warnings and precautions for use

Monitoring

Before treatment

Before starting treatment with AUBAMIDE 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 AUBAMIDE the following should be monitored:

• Blood pressure- to be checked periodically

• Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)

• Serum aminotransaminase should be assessed 6 months before treatment on AUBAMIDE is initiated.

• ALT levels should be monitored at least monthly for six months after starting treatment on AUBAMIDE.

• Liver enzymes should be monitored during the first 6 months of treatment and 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.

• 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 6 months to reach plasma concentrations less than 0.25 µg/mL, however, 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

AUBAMIDE (see **sections 4.6** and **5.2** for procedural details).

Hepatic effects

Elevations of liver enzymes have been observed in patients receiving AUBAMIDE (see **section 4.8**). These elevations occurred mostly within the first 6 months of treatment. Serum aminotransaminase and bilirubin levels should be obtained within 6 months before initiating therapy with AUBAMIDE. Observe ALT levels at least monthly for six months after starting treatment on AUBAMIDE. Liver function should be monitored when AUBAMIDE is given with other potentially hepatotoxic medication. AUBAMIDE therapy should be discontinued if liver injury is suspected; consider discontinuing AUBAMIDE therapy if elevated liver enzymes (greater than 3-fold ULN) are confirmed and start an accelerated elimination procedure (see **section 4.9**).

Patients with pre-existing liver disease and /or who consume substantial quantities of alcohol may be at increased risk of developing elevated liver enzymes when taking AUBAMIDE and should be closely monitored for signals of liver disease.

Hypoproteinaemia

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

Blood pressure

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

Infections

Initiation of treatment with AUBAMIDE should be delayed in patients with a severe active infection until it is resolved.

Based on the immunomodulatory effect of AUBAMIDE, if a patient develops a serious infection, suspending treatment with AUBAMIDE should be considered and the risks and benefits 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 AUBAMIDE should be instructed to report symptoms of infections to a medical practitioner. Patients with active acute or chronic infections should not start treatment with AUBAMIDE until the infection(s) is resolved.

The safety of AUBAMIDE 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 AUBAMIDE.

Respiratory reactions

Interstitial lung disease (ILD) has been reported with teriflunomide in the post marketing setting.

ILD and worsening of pre-existing ILD have been reported during treatment with leflunomide, the parent compound of teriflunomide. The risk is increased in patients who had a history of ILD when treated with leflunomide.

ILD may occur acutely at any time during therapy with a variable clinical presentation. ILD may be fatal. New onset or worsening pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, where appropriate. If discontinuation of the medicinal product is necessary, initiation of an accelerated elimination procedure should be considered (see **section 4.9**).

Haematological effects

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

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

AUBAMIDE 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 been reported as well.

In case of ulcerative stomatitis, AUBAMIDE 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), AUBAMIDE and any other possibly associated treatment must be discontinued, and an accelerated elimination procedure must be initiated immediately. In such cases, patients should not be re-exposed to AUBAMIDE (see **section 4.3**).

Peripheral neuropathy

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

Vaccination

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

Immunosuppressive or immunomodulating therapies

While leflunomide is the parent compound of teriflunomide, co-administration of AUBAMIDE with leflunomide is contraindicated.

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. The long-term safety of these combinations in the treatment of multiple sclerosis has not been established.

Switching to or from AUBAMIDE

According to the clinical data on concomitant administration of teriflunomide with interferon beta or glatiramer acetate, a waiting period is not necessary when starting AUBAMIDE treatment before or after therapy on interferon beta or glatiramer acetate. Natalizumab has a long half-life, hence caution should be taken when initiating therapy with AUBAMIDE. Concomitant immune effects could occur up to 3 months after natalizumab treatment has been stopped.

A 6-week waiting period is required after treatment on fingolimod, to allow for clearance from the blood circulation. A 1 to 2 month waiting period is required for the lymphocytes to return to the normal range after fingolimod treatment. Initiating AUBAMIDE therapy during this period should be done with great caution.

If teriflunomide treatment is discontinued and other therapies are initiated within 3,5 months, concomitant exposure may occur. Caution should be taken in this case.

Lactose

Since AUBAMIDE tablets contain lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take AUBAMIDE .

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions of other substances on teriflunomide

The primary biotransformation pathway for AUBAMIDE is hydrolysis, with oxidation being a minor pathway. There is also limited involvement of cytochrome P450 (CYP) or flavin monoamine oxidase enzymes.

According to in-vitro studies, AUBAMIDE is a substrate of the efflux transporter BCRP. BCRP inhibitors such as ciclosporin, eltrombopag, gefitinib may increase exposure of AUBAMIDE.

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, phenobarbitone, phenytoin and St John's Wort should be used with caution during treatment with AUBAMIDE.

Cholestyramine or activated charcoal

It is not recommended that patients receiving AUBAMIDE be treated with c*h*olestyramine or activated charcoal as this leads to a rapid and significant decrease in plasma concentration unless an accelerated elimination is desired.

Pharmacokinetic interactions of teriflunomide on other substances

Effect of teriflunomide on CYP2C8 substrate: repaglinide

There was an increase in mean repaglinide C_{max} and AUC (1,7- and 2,4-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo.

Therefore, medicinal products metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during treatment with AUBAMIDE.

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 AUBAMIDE.

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 AUBAMIDE may be a weak inducer of CYP1A2 *in vivo*. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetin, theophylline and tizanidine) should be used with caution during treatment with AUBAMIDE, 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 co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered with AUBAMIDE, 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 AUBAMIDE is co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, 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, the recommended dose for co-administration with AUBAMIDE should not exceed 10 mg once daily. 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 AUBAMIDE should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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 medical practitioner.

Use in males

The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low . Nonetheless, patients should be advised on the use of barrier contraception.

Pregnancy

There is a 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**).

Patients must be advised that if they suspect pregnancy, they must notify the physician immediately and test for pregnancy. If the test is positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of teriflunomide through the accelerated elimination procedure on 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.

Teriflunomide plasma concentrations should be measured before a woman attempts 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 at least 14 days. If both plasma concentrations are below 0,02 mg/L, there is no risk to be expected on the foetus.

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 orally for a period of 11 days.

However, after the elimination procedure two verification tests should be done 14 days apart. A waiting period of one-and-a-half months between the first incident of a plasma concentration below 0,02 mg/L and conception is required.

Cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens. 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. AUBAMIDE is contraindicated during breast-feeding (see **section 4.3**).

Fertility

Animal study results have not shown an effect on fertility (see **section 5.3**). However, though human data is lacking, no effect on male and female fertility is anticipated.

4.7 Effects on ability to drive and use machines

AUBAMIDE 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

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

The side effects are as follows: very common and common = Frequent; Uncommon, rare and very rare = less frequent and 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	Frequent	Less frequent	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
Blood and lymphatic system disorders	Neutropenia, Anaemia	Mild thrombocytopenia (platelets < 100 G/l)	-
Immune system disorders	Seasonal allergic reactions	-	Hyper-sensitivity reactions (immediate or delayed) including anaphylaxis and angioedema
Psychiatric disorders	Anxiety	-	-
Nervous system disorders	Headache, Paraesthesia, Sciatica, Carpal tunnel syndrome	Peripheral neuropathy	-
	Hyperaesthesia, Neuralgia	-	-

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
Hepatobiliary disorders	Alanine aminotransferase (ALT) increase, Gamma-glutamyltransferase (GGT) increase, Aspartate aminotransferase increase	-	Acute hepatitis
Metabolism and nutrition disorders	-	-	Dyslipidaemia
Skin and subcutaneous tissue disorders	Alopecia, Rash, Acne	Nail disorders	Severe skin reactions
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, Myalgia, Arthralgia	-	-
Renal and urinary disorders	Pollakiuria	-	-
Reproductive system and breast disorders	Menorrhagia	-	-
General disorders and administration site conditions	Pain, Asthenia	-	-

Investigations	Increased alanine aminotransferase, Weight decrease, Neutrophil count decrease, White blood cell count decrease, increased gamma- glutamyltransferase, increased aspartate aminotransferase	-	-
Injury, poisoning and procedural complications	Post-traumatic pain	-	-

Description of selected adverse reactions

Alopecia

Alopecia was reported as hair thinning, decreased hair density, hair loss, associated or not with hair texture change. 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.

Hepatic effects

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, there was an increase in the systolic and diastolic blood pressure for patients given teriflunomide as compared to the patients given who received the placebo medicine. Hypertension was reported as an adverse reaction in patients treated with teriflunomide.

Infections

In placebo-controlled studies, no increase in serious infections was observed with teriflunomide 14 mg as compared to placebo.

Haematological effects

A mean decrease affecting white blood cell (WBC) count (<15 % from baseline levels, mainly neutrophil and lymphocytes decrease) was observed in placebo-controlled trials with teriflunomide, however, 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).

Peripheral neuropathy

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g. carpal tunnel syndrome), were commonly reported in patients taking teriflunomide than in patients taking placebo. In placebo-controlled studies, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.9 % on 14 mg of teriflunomide, compared with 0.4 % 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 medicines 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, frequencies for asthenia were 2,0 % and 2,2 % in the placebo 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.0 Adverse**

Drug Reactions Reporting Form", found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8. Side effects may also be reported directly to Cipla Medpro (Pty) Ltd: drugsafetysa@cipla.com.

4.9 Overdose

Symptoms

There is no experience regarding teriflunomide overdose or intoxication in humans.

Management

In the event of an 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), required for the de novo pyrimidine synthesis. As a consequence, teriflunomide blocks 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

Teriflunomide 14 mg once a day led to a mild mean reduction in lymphocyte count, 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 QT study performed in healthy subjects, teriflunomide at average 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. In addition, no QTcF values were ≥ 480 ms and no changes from baseline were > 60 ms.

Effect on renal tubular functions

In the placebo-controlled studies, average decreases in serum uric acid at a range of 20 to 30 % were observed in patients treated with teriflunomide compared to placebo. The average 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 obligation to submit the results of studies with teriflunomide in one or more subsets of the paediatric population in multiple sclerosis (see **section 4.2** for information on paediatric use) was deferred as use in this age group is not recommended.

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

From the mean predicted pharmacokinetic parameters calculated from the population pharmacokinetic 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 (11 litres) after a single intravenous (IV) administration.

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

Biotransformation

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

Elimination

Teriflunomide is excreted in the gastrointestinal tract, mainly through the bile as unchanged 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 a 21-day period, approximately 60,1 % of the administered dose is excreted via feces and urine. After the rapid elimination procedure with cholestyramine, an additional 23,1 % was recovered (mostly in faeces).

Based on individual prediction of pharmacokinetic parameters using the population pharmacokinetics (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.

After discontinuing teriflunomide therapy and initiating the administration of cholestyramine 8 g three times a day, the plasma concentration of teriflunomide is reduced by 52 % at the end of day one, 91 % at the end of day three, 99,2 % at the end of day seven, and 99,9 % at the completion of day eleven. 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 of 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 Pop PK analysis: age, body weight, gender, race, and albumin and bilirubin levels. Nevertheless, their impact remains limited (≤31 %).

Hepatic impairment

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

Renal impairment

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

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

lactose monohydrate

maize starch

hydroxypropyl cellulose

microcrystalline cellulose

sodium starch glycolate (Type A)

colloidal silicon dioxide

magnesium stearate

Tablet coating

Opadry yellow (03B520087)

Hypromellose (E464)

titanium dioxide (E171)

macrogol (E1521)

iron oxide yellow (E172)

iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store at or below 25°C

6.5 Nature and contents of container

Blister pack comprised of plain aluminium foil/PVC film as the forming material and plain aluminum foil as the lidding material. Film-coated tablets are packed into 10's per blister set and the three blisters are further packed in plain cartons to make 30 tablets in each carton.

Film-coated tablets packed in 100's are packaged into 60cc HDPE round, white opaque screw neck child resistant closure bottles with liner (CR-02).

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. HOLDER OF CERTIFICATE OF REGISTRATION

Cipla Medpro (Pty) Ltd

Building 9, Parc du Cap

Mispel Street, Bellville

Cape Town, 7530

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Customer Care: 080 222 6662

8. REGISTRATION NUMBER

55/32.12/0228

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10. DATE OF REVISION OF THE TEXT

Not applicable