Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TERITEMSO, 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 TERITEMSO because recommended doses of TERITEMSO and leflunomide result in a similar range of plasma concentrations of teriflunomide. Obtain transaminase and bilirubin levels within 6 months before initiation of TERITEMSO and monitor ALT levels at least monthly for six months. If medicine induced liver injury is suspected, discontinue TERITEMSO and start accelerated elimination procedure.

Risk of Teratogenicity:

Based on animal data, teriflunomide may cause major birth defects if used during pregnancy. TERITEMSO is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during TERITEMSO treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TERITEMSO: Each film-coated tablet contains 14 mg of teriflunomide.

Excipient(s) with known effect: Each film-coated tablet contains 83,4 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets. The film-coated tablet should not be divided.

Blue coloured, pentagonal shaped, biconvex, film-coated tablets, debossed with "14" on one side and “T” on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TERITEMSO is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of relapses and to delay the accumulation of physical disability.

4.2 Posology and method of administration

Posology

The treatment should be initiated and supervised by a medical practitioner experienced in multiple sclerosis.

The recommended dose of **TERITEMSO** is 14 mg orally once daily.

Special populations

Elderly population

TERITEMSO 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.

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

Paediatric population:

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

Method of administration

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

4.3 Contraindications

- Hypersensitivity to teriflunomide or to any of the excipients of **TERITEMSO** listed in section 6.1.
- Patients with severe hepatic impairment (Child-Pugh class C).
- As leflunomide is the parent compound of teriflunomide, co-administration of **TERITEMSO** with leflunomide is not recommended (see section 4.4).
- **TERITEMSO** is contraindicated for women during pregnancy or women of childbearing potential who are not on reliable contraception (see section 4.6).
- Breastfeeding women (see section 4.6).
- Patients with severe immunodeficiency states, e.g. acquired immunodeficiency syndrome (AIDS).
- Patients with significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia or thrombocytopenia.
- Patients with severe active infection until resolution (see section 4.4).
- Patients with severe renal impairment undergoing dialysis, because insufficient clinical

experience is available in this patient group.

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

4.4 Special warnings and precautions for use

Monitoring

Before treatment

Before starting treatment with **TERITEMSO** 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 **TERITEMSO** the following should be monitored:

- Blood pressure
  - Check periodically
- Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)
  - Liver enzymes should be assessed 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.
- 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 **TERITEMSO** (see sections 4.6 and 5.2).

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.
TERITEMSO should be discontinued if liver injury is suspected; consider discontinuing **TERITEMSO** therapy if the ALT exceeds 3-times ULN and this is confirmed within 48 hours.
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 teriflunomide and should be closely monitored for signals of liver disease.

Hypoproteinaemia

Since teriflunomide as contained in **TERITEMSO**, 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.
TERITEMSO should not be used in patients with conditions of severe hypoproteinaemia.

Blood pressure

Elevation of blood pressure may occur during treatment with **TERITEMSO** (see section 4.8).
Check blood pressure before start of **TERITEMSO** and periodically thereafter. Blood pressure elevation should be appropriately managed during treatment with **TERITEMSO**.

Infections

Based on the immunomodulatory effect of **TERITEMSO**, if a patient develops a serious infection, consider suspending treatment with **TERITEMSO** and reassess the benefits and risks prior to re-initiation of therapy.

Due to the prolonged half-life, accelerated elimination with cholestyramine or charcoal may be considered.

Instruct patients receiving **TERITEMSO** to report symptoms of infections to a medical practitioner.

Patients with active acute or chronic infections should not start treatment with **TERITEMSO** until the infection(s) is resolved.

The safety of **TERITEMSO** 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 **TERITEMSO**.

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, as appropriate. If discontinuation of the medicine is necessary, initiation of an accelerated elimination procedure should be considered.

Haematological effects

A mean decrease of 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 with **TERITEMSO** and the complete blood cell count should be assessed during **TERITEMSO** therapy as indicated by clinical signs and symptoms (e.g., infections).

In patients with pre-existing anaemia, leukopenia, and /or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of haematological disorders is increased. If such effects occur, the accelerated elimination procedure (see above) to reduce plasma levels of teriflunomide should be considered.
In cases of severe haematological reactions, including pancytopenia, **TERITEMSO** 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, cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported.
In case of ulcerative stomatitis, **TERITEMSO** 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), **TERITEMSO** 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 **TERITEMSO** (see section 4.3).
New onset of psoriasis (including pustular psoriasis) and worsening of pre-existing psoriasis have been reported during the use of **TERITEMSO**. 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 **TERITEMSO** (see section 4.8). Most patients improved after discontinuation of **TERITEMSO**. 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 **TERITEMSO** develops a confirmed peripheral neuropathy, consider discontinuing **TERITEMSO** therapy and performing the accelerated elimination procedure.

Vaccination

Reports from 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 and immunomodulating therapies

As leflunomide is the parent compound of teriflunomide, co-administration of **TERITEMSO** with leflunomide is contraindicated (see section 4.3).

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 other immune modulating therapies for up to one year (interferon beta, glatiramer acetate) 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 TERITEMSO

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 **TERITEMSO** was immediately started. Therefore, caution is required when switching patients from natalizumab

to **TERITEMSO**.

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

Interference with determination of ionised calcium levels

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

Excipients with known effect

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **TERITEMSO**.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions of other medicines on **TERITEMSO**

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 (phenobarbitone), phenytoin and St John's Wort should be used with caution during the treatment with **TERITEMSO**.

Cholestyramine or activated charcoal

It is recommended that patients receiving **TERITEMSO** 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 **TERITEMSO** on other medicine

*Effect of **TERITEMSO** 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 **TERITEMSO**, suggesting that **TERITEMSO** is an inhibitor of CYP2C8 *in vivo*. Therefore, medicines metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during treatment with **TERITEMSO**.

*Effect of **TERITEMSO** 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 **TERITEMSO** 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 **TERITEMSO**.

*Effect of **TERITEMSO** 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, medicines metabolised by CYP1A2 (such as duloxetine, alosetron, theophylline and tizanidine) should be used with caution during treatment with **TERITEMSO**, as it could lead to the reduction of the efficacy of these medicines.

*Effect of **TERITEMSO** on warfarin*

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

*Effect of **TERITEMSO** 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 **TERITEMSO** is co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, and zidovudine, caution is recommended.

*Effect of **TERITEMSO** 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 **TERITEMSO**. 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 **TERITEMSO**. 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 **TERITEMSO** should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicines and reduction of the dose of these medicines should be considered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Use in males

The risk of male-mediated embryo-foetal toxicity through **TERITEMSO** treatment is considered low; however, patients should be advised to use barrier contraception (see section 5.3).

Use in females

TERITEMSO is contraindicated in women of childbearing potential not using reliable contraceptives (see section 4.3). Women of childbearing potential must use effective contraception during treatment and after treatment as long as **TERITEMSO** 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.

Pregnancy

TERITEMSO is contraindicated during pregnancy (see section 4.3).

There are no adequate and well-controlled studies of **TERITEMSO** in pregnant women. However, based on animal studies, teriflunomide may increase the risk of fetal death or teratogenic effects when administered to pregnant women.

Human teriflunomide plasma concentration less than 0,02 µg/mL is expected to have minimal risk based on available animal data. If **TERITEMSO** is to be discontinued, an accelerated elimination procedure is recommended (see sections 4.4 and 5.2). Without the accelerated elimination procedure, on average it takes 6 months to reach plasma concentrations less than 0,02 µg/mL. Due to individual variation in medicines clearance, teriflunomide plasma concentrations may need to be checked for up to 2 years after discontinuation. The accelerated elimination could be used at any time after discontinuation of **TERITEMSO**.

Breastfeeding

Animal studies have shown excretion of teriflunomide in milk. **TERITEMSO** is contraindicated during breastfeeding (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

TERITEMSO 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

a. Summary of the safety profile

The most frequent reported adverse reactions in treated patients were influenza, upper respiratory tract infection, urinary tract infection, paraesthesia, headache, diarrhoea, increased ALT, nausea, and alopecia. These side effects are usually mild to moderate, transient and infrequently leads to treatment discontinuation.

b. Tabulated list of adverse reactions

Infections and infestations	
Frequent:	Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, viral gastroenteritis, oral herpes, tooth infection, laryngitis, tinea pedis
Frequency not	Severe infections including sepsis[a]

known:	
Blood and lymphatic system disorders	
Frequent:	Neutropenia[b], anaemia
Less frequent:	Mild thrombocytopenia (platelets < 100 G/l)
Immune system disorders	
Frequent:	Mild allergic reactions, seasonal allergy
Frequency not known:	Hypersensitivity reactions (immediate or delayed) including anaphylaxis and angioedema
Metabolism and nutrition disorders	
Frequency not known:	Dyslipidaemia
Psychiatric disorders	
Frequent:	Anxiety
Nervous system disorders	
Frequent:	Headache, paraesthesia, sciatica, carpal tunnel syndrome, hyperaesthesia, neuralgia
Less frequent:	Peripheral neuropathy
Cardiac disorders	
Frequent:	Palpitations
Vascular disorders	
Frequent:	Hypertension[b]
Respiratory, thoracic and mediastinal disorders	
Frequency not known:	Interstitial lung disease
Gastrointestinal disorders	

Frequent:	Diarrhoea, nausea, upper abdominal pain, vomiting, toothache
Frequency not known:	Pancreatitis, stomatitis
Hepato-biliary disorders	
Frequent:	Alanine aminotransferase (ALT) increase[b], gamma glutamyl transferase (GGT) increase[b], aspartate aminotransferase increase[b]
Frequency not known:	Acute hepatitis
Skin and subcutaneous tissue disorders	
Frequent:	Alopecia, rash, acne
Less frequent:	Nail disorders
Frequency not known:	Severe skin reactions[a], psoriasis (including pustular)[b]
Musculoskeletal and connective tissue disorders	
Frequent:	Musculoskeletal pain, myalgia, arthralgia
Renal and urinary disorders	
Frequent:	Pollakiuria
Reproductive system and breast disorders	
Frequent:	Menorrhagia
General disorders and administration site conditions	
Frequent:	Pain, asthenia[a]
Investigations	
Frequent:	Weight decrease, neutrophil count decrease[b], white blood cell count decrease[b], blood creatine phosphokinase increased

Injury, poisoning and procedural complications	
Less frequent:	Post-traumatic pain

[a]: please refer to the detailed description section

[b]: see section 4.4

c. Description of selected adverse reactions

Alopecia

Alopecia is reported as hair thinning, decreased hair density, hair loss, associated or not with hair texture change. It may occur more frequently as diffuse or generalised over the scalp (no complete hair loss) and more often during the first 6 months of treatment.

Hepatic effects

Mild increases in transaminase, alanine aminotransferase (ALT), may occur in patients taking teriflunomide. These elevations in transaminase occurs mostly within the first 6 months of treatment and are reversible after treatment cessation. The recovery time varies between months and years.

Blood pressure effects

Patients taking teriflunomide may have a slight increase in blood pressure.

Infections

The occurrence of serious opportunistic infections after taking teriflunomide are not frequent, but severe infections including sepsis, sometimes fatal, have been reported post-marketing.

Haematological effects

Patients may have a slight decrease in white blood cell (WBC) count after taking teriflunomide which may occur during the first 6 weeks and then stabilise over time while on treatment, but at decreased levels.

The effect on red blood cell (RBC) and platelet counts are less pronounced.

Peripheral neuropathy

Peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), may occur in patients taking teriflunomide. Recovery is likely after treatment is stopped.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

The risk of malignancy, particularly lymphoproliferative disorders, is increased with concomitant use of teriflunomide with other medicines that affect the immune system (class effect).

Severe skin reactions

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

Asthenia

Asthenia may occur in patients taking teriflunomide.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

There is no experience regarding **TERITEMSO** overdose or intoxication in humans.

Management:

In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination.

Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 4 g cholestyramine three times a day, 8 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. 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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Teriflunomide is an immunomodulatory medicine with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. Therefore, teriflunomide reduces the activation and 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.

Slowly dividing or resting cells which rely on the salvage pathway for pyrimidine synthesis are

unaffected by teriflunomide.

It is likely that teriflunomide diminishes in periphery the numbers of activated lymphocytes available to migrate into the central nervous system (CNS).

Pharmacodynamic effects

Immune system

Effects on immune cell numbers in the blood: In the placebo-controlled studies, teriflunomide 14 mg once a day led to a mild mean reduction in lymphocyte count, of less than 0,3 x 10^9/l, which occurred over the first 3 months of treatment and levels were maintained until the end of the treatment.

Potential to prolong the QT interval

In a placebo-controlled thorough QT study performed in healthy subjects, teriflunomide at mean steady-state concentrations did not show any potential for prolonging the QTcF interval compared with placebo: the largest time matched mean difference between teriflunomide and placebo was 3,45 ms with the upper bound of the 90% CI being 6,45 ms.

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, 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.

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.

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 medicine and most likely by direct secretion. Teriflunomide is a substrate of the efflux transporter BCRP, which could be involved in direct secretion. Over 21 days, 60,1 % of the administered dose is excreted via faeces (37,5 %) and urine (22,6 %). After the rapid elimination procedure with cholestyramine, an additional 23,1 % was recovered (mostly in faeces). Based on individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, median $t_{1/2z}$ was approximately 19 days after repeated doses of 14 mg. After a single intravenous administration, the total body clearance of teriflunomide is

30,5 mL/h.

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 pharmacokinetics 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 pharmacokinetics of teriflunomide. Therefore, no dose adjustment is anticipated in mild, moderate and severe renal impaired patients.

5.3 Preclinical safety data

Repeated oral administration of teriflunomide to mice, rats and dogs for up to 3, 6, and 12 months, respectively, revealed that the major targets of toxicity were the bone marrow, lymphoid organs,

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

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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal silicon dioxide

Corn starch/maize starch

Hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Sodium starch glycolate

Tablet coating: Opadry Blue 03F505097

Hypromellose 2910

Indigo carmine aluminium lake/FD&C blue #2

Iron oxide yellow

Macrogol/PEG

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

2 blisters per carton, 14 film-coated tablets per blister. 28 film-coated tablets per carton.

Alu-Alu blister pack comprises of cold formable foil and Hard Tempered Aluminium foil coated with heat seal lacquer on the sealing side and dull finish on the other side. Alu-Alu blister packs are packed into printed carton along with leaflet.

6.6 Special precautions for disposal and other handling

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

requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand

1685

South Africa

8. REGISTRATION NUMBER(S)

55/32.16/0244

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 June 2023

10. DATE OF REVISION OF THE TEXT

Not applicable