PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

AUBAGIO® 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 AUBAGIO because recommended doses of AUBAGIO and leflunomide result in a similar range of plasma concentrations of AUBAGIO. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO and monitor alanine aminotransferase (ALT) levels at least monthly for six months. If drug-induced liver injury is suspected, discontinue AUBAGIO and start accelerated elimination procedure. Concomitant use of AUBAGIO with other potentially hepatotoxic medicines may increase the risk of severe liver injury.

Risk of teratogenicity:

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 14 mg of teriflunomide.

Contains sugar (76 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side (dose strength given as number 14) and engraved with corporate logo on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUBAGIO is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease 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 AUBAGIO is 14 mg orally once daily.

AUBAGIO can be taken with or without food.

Special populations

Elderly:

AUBAGIO has not been specifically studied in the elderly (over 65 years of age).

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.

AUBAGIO is contraindicated in patients with severe hepatic impairment.

Paediatric population:

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

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to teriflunomide, leflunomide or to any of the excipients (see section 6.1).
- Patients with severe hepatic impairment.
- As leflunomide is the parent compound of teriflunomide, co-administration of AUBAGIO with leflunomide is not recommended.
- AUBAGIO is contraindicated in women during pregnancy or women of childbearing potential who are not on reliable contraception during treatment with AUBAGIO and thereafter, as long as its plasma levels are above 0,02 µg/mL (see section 4.6).

4.4 Special warnings and precautions for use

Hepatic effects:

Elevations of liver enzymes have been observed in patients receiving AUBAGIO.

In placebo-controlled trials, alanine aminotransferase (ALT) greater than three times the upper limit of normal (ULN) occurred in 62/1 002 (6,2 %) of patients on AUBAGIO and 38/997 (3,8 %) of patients on placebo, during the treatment period. These elevations occurred mostly within the first 6 months of treatment. Half of the cases returned to normal without medicine discontinuation. In clinical trials, teriflunomide was discontinued if the ALT elevation exceeded 3 times the ULN twice. Serum transaminase levels returned to normal within approximately 2 months after

discontinuation of AUBAGIO.

One additional clinically significant case of “toxic hepatitis” was reported in a 35-year-old female patient. Although the aetiology of the hepatic event remained unclear, a causal role of AUBAGIO in this case is possible.

Cases of drug-induced liver injury (DILI) have been observed in the post-marketing setting, sometimes life-threatening, often in combination with other hepatotoxic medicines.

Obtain serum transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO. Consider monitoring when AUBAGIO is given with other potentially hepatotoxic medicines. Consider discontinuing AUBAGIO if serum transaminase increase (greater than three times the ULN) is confirmed. Monitor serum transaminase and bilirubin on AUBAGIO therapy, particularly in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. If liver injury is suspected to be AUBAGIO-induced, discontinue AUBAGIO and start an accelerated elimination procedure (see section 4.9) and monitor liver tests weekly until normalised.

If teriflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of AUBAGIO therapy may be considered.

Usage in women of childbearing potential / during pregnancy:

Animal data suggest risks to the fetus. Women of childbearing potential must use effective contraception to avoid pregnancy while taking AUBAGIO.

If AUBAGIO is stopped, women should continue contraception until teriflunomide plasma concentrations have been checked to be equal to 0,02 µg/mL or lower.

Women who are pregnant or planning to become pregnant, should be advised that an accelerated elimination procedure can be used to quickly decrease the plasma concentration of teriflunomide. Without the accelerated elimination procedure, on average it takes 8 months to reach plasma

concentrations less than or equal to 0,02 µg/mL. However, due to individual variation in clearance it may take up to 2 years.

The accelerated elimination could be used at any time after discontinuation of AUBAGIO (see section 4.9).

Blood pressure effects:

In placebo-controlled studies, mean change from baseline to endpoint value in systolic blood pressure was 2,7 mm Hg for AUBAGIO and 0,6 mm Hg for the placebo. The change from baseline in diastolic blood pressure was 1,9 mm Hg for AUBAGIO and -0,3 mm Hg for the placebo. Hypertension was reported as an adverse reaction in 4,3 % of patients treated with AUBAGIO, compared with 1,8 % on the placebo. Check blood pressure before the start of AUBAGIO treatment and periodically thereafter.

Blood pressure elevation should be appropriately managed during treatment with AUBAGIO.

Infections:

In placebo-controlled studies of AUBAGIO, no overall increase in the risk of serious infections was observed with teriflunomide (2,7 %) compared to placebo (2,2 %). However, one fatal case of *Klebsiella pneumoniae* sepsis occurred in a patient taking AUBAGIO for 1,7 years. In clinical studies with AUBAGIO, cytomegalovirus hepatitis reactivation and tuberculosis have been observed.

However, based on the immunomodulatory effect of AUBAGIO, if a patient develops a serious infection, consider suspending treatment with AUBAGIO and reassess the benefits and risks prior to re-initiation of therapy. Due to the prolonged half-life, accelerated elimination with colestyramine or charcoal may be considered.

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

Patients with active acute or chronic infections should not start treatment with AUBAGIO until the

infection(s) is resolved. AUBAGIO is not recommended with severe immunodeficiency, bone marrow disease, or severe uncontrolled infections.

The safety of AUBAGIO in individuals with latent tuberculosis infection is unknown, as tuberculosis screening was not systematically performed in clinical studies. Patients testing positive in tuberculosis screening, should be treated according to standard medical practice prior to therapy with AUBAGIO.

Respiratory effects:

Interstitial lung disease, including acute interstitial pneumonitis, has been reported with AUBAGIO in the post-marketing setting.

Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during treatment with leflunomide. Interstitial lung disease may occur acutely at any time during therapy, with a variable clinical presentation. Interstitial lung disease may be fatal. New onset or worsening pulmonary symptoms, such as cough and dyspnoea, with or without associated fever, may be a reason for discontinuation of the therapy and for further investigation as appropriate. If discontinuation of AUBAGIO therapy is necessary, consider initiation of an accelerated elimination procedure (see section 4.9).

Haematological effects:

A mean decrease in white blood cell (WBC) count of approximately 15 % (mainly neutrophils and lymphocytes) and in platelet counts of approximately 10 % was observed in placebo-controlled trials with AUBAGIO as compared to baseline. The decrease in mean WBC count occurred during the first 6 weeks and WBC count remained low during treatment. In placebo-controlled studies, neutrophil count < 1,5 x 10^9/L was observed in 16 % of patients on AUBAGIO, compared with 7 % of patients on placebo; lymphocyte count < 0,8 x 10^9/L was observed in 12 % of patients on AUBAGIO compared with 6 % of patients on placebo.

At baseline, a recent blood cell count should be available before the initiation of treatment with AUBAGIO and assessed during AUBAGIO therapy. Further monitoring should be based on signs and symptoms suggestive of infection.

Vaccination:

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

Skin reactions:

Severe cutaneous adverse reactions (SCARs)

Cases of serious skin reactions, sometimes fatal, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with teriflunomide.

If skin and/or mucosal reactions (ulcerative stomatitis) are observed which raise the suspicion of severe generalised major skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis – Lyell's syndrome, or drug reaction with eosinophilia and systemic symptoms), AUBAGIO and any other possibly associated treatment must be discontinued, and an accelerated elimination procedure initiated immediately. In such cases patients should not be re-exposed to teriflunomide (see section 4.9).

Peripheral neuropathy:

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

Concomitant use of immunosuppressive or immunomodulating therapies:

As leflunomide is the parent compound of teriflunomide, co-administration of AUBAGIO with leflunomide is contraindicated.

Co-administration with antineoplastic or immunosuppressive therapies used for treatment of MS has not been evaluated.

Safety studies, in which AUBAGIO was concomitantly administered with other immune modulating therapies for up to one year (interferon beta, glatiramer acetate) did not reveal any specific safety concerns. The long-term safety of these combinations in the treatment of multiple sclerosis has not been established.

Elimination procedure:

Teriflunomide is slowly eliminated from the plasma.

When desired, an accelerated elimination procedure can be used (see section 4.9).

Lactose:

Since AUBAGIO tablets contain lactose, patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take AUBAGIO.

4.5 Interaction with other medicines and other forms of interaction

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

Potential for other medicines to affect AUBAGIO:

Based on *in vitro* studies, teriflunomide is a substrate of the efflux transporter BCRP. BCRP inhibitors (such as ciclosporin, eltrombopag, gefitinib) may increase exposure of teriflunomide.

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] and AUBAGIO (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 AUBAGIO.

Potential for AUBAGIO to affect other medicines:

Effect of AUBAGIO on CYP2C8 substrates:

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

The magnitude of interaction could be higher at the recommended repaglinide dose. Therefore, monitoring patients with concomitant use of medicines metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone is recommended as they may have higher exposure.

Effect of AUBAGIO on oral contraceptives:

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 AUBAGIO.

While this interaction of AUBAGIO is not expected to adversely impact the efficacy of oral contraceptives, consideration should be given to the type or dose of oral contraceptives used in combination with AUBAGIO.

Effect of AUBAGIO on CYP1A2 substrates:

Repeated doses of AUBAGIO decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18 % and 55 %, respectively, suggesting that AUBAGIO may be a weak inducer of CYP1A2 *in vivo*.

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

Effect of AUBAGIO on warfarin:

A 25 % decrease in peak international normalised ratio (INR) was observed when AUBAGIO was co-administered with warfarin as compared with warfarin alone.

Therefore, when warfarin is co-administered with AUBAGIO, close INR follow-up and monitoring is recommended.

Effect of AUBAGIO 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 AUBAGIO is co-administered with substrates of OAT3, such as cefaclor, penicillin G, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate or zidovudine, caution should be observed.

Effect of AUBAGIO 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 AUBAGIO. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. If used together, the dose of rosuvastatin 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-CoA reductase inhibitors (e.g. simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration of AUBAGIO should also be undertaken with caution. Monitor patients closely for signs and symptoms of excessive exposure to these medicines and consider reduction of the dose of these medicines.

Effect of AUBAGIO on CYP2B6, CYP3A, CYP2C9, CYP2C19 and CYP2D6 substrates:
AUBAGIO did not affect the pharmacokinetics of bupropion (a CYP2B6 substrate), midazolam (a CYP3A substrate), *S*-warfarin (a CYP2C9 substrate), omeprazole (a CYP2C19 substrate) and metoprolol (a CYP2D6 substrate).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies of AUBAGIO in pregnant women. However, based on animal studies, AUBAGIO may increase the risk of fetal death or teratogenic effects when administered to pregnant women.
AUBAGIO is contraindicated during pregnancy and in women of childbearing potential not using reliable contraception (see section 4.3).
Human teriflunomide plasma concentration less than 0,02 µg/mL is expected to have minimal risk based on available animal data. If AUBAGIO is to be discontinued, an accelerated elimination procedure is recommended (see sections 4.4 and 4.9).

Use in males

The risk of male-mediated embryo-fetal toxicity through AUBAGIO treatment is considered low, however patients should be advised to use barrier contraception.

Breastfeeding

Mothers must not breastfeed their infants while taking AUBAGIO.
Animal studies have shown excretion of AUBAGIO in breast milk.

4.7 Effects on ability to drive or use machines

AUBAGIO has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

A total of 2 047 patients on AUBAGIO and 997 on placebo constituted the safety population in the pooled analysis of placebo-controlled studies in patients with relapsing forms of MS (RMS).
In clinical trials, the most frequent adverse reactions for AUBAGIO (incidence ≥ 10 %) in the placebo-controlled studies were headache, diarrhoea, nausea, alopecia and increased ALT.

b. Tabulated list of adverse reactions

Adverse reactions reported with AUBAGIO 14 mg in placebo-controlled studies are shown below.
Frequencies were defined using the following convention when applicable: 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).
Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**
Infections and infestations		Upper respiratory tract infection, influenza, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, viral gastroenteritis, oral herpes, tooth infection, laryngitis, tinea pedis
Blood and lymphatic system disorders		Neutropenia

Immune system disorders		Mild allergic reactions, seasonal allergy
Psychiatric disorders		Anxiety
Nervous system disorders	Headache	Paraesthesia, sciatica, carpal tunnel syndrome, hyperaesthesia, neuralgia
Cardiac disorders		Palpitations
Vascular disorders		Hypertension
Gastrointestinal disorders	Diarrhoea, nausea	Upper abdominal pain, vomiting, toothache
Skin and subcutaneous tissue disorders	Alopecia*	Rash, acne
Musculoskeletal and connective tissue disorders		Arthralgia, musculoskeletal pain, myalgia
Renal and urinary disorders		Pollakiuria
Reproductive system and breast disorders		Menorrhagia
General disorders and administration site conditions		Pain
Investigations	Increased alanine aminotransferase (ALT)	Increased aspartate aminotransferase (AST), increased gamma-glutamyltransferase (GGT), decreased weight, decreased neutrophil count, increased blood creatine phosphokinase, decreased white blood cell count

Injury, poisoning and procedural complications		Post-traumatic pain

c. 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 15,2 % of patients treated with 14 mg AUBAGIO versus 4,3 % in patients treated with placebo.

Most cases were described as diffuse or generalised over the scalp and were more likely to occur during the first 6 months.

Polyneuropathy:

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g. carpal tunnel syndrome), was reported more frequently in patients taking AUBAGIO 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) on doses of 14 mg of AUBAGIO, compared with 0,4 % on placebo (4 patients). Treatment was discontinued in 5 patients with confirmed neuropathy. Recovery following treatment discontinuation was reported in 4 of these patients.

Post-marketing experience (spontaneous reports)

In post-marketing experience with AUBAGIO, the following adverse reactions have been identified:

Immune system disorders:

Hypersensitivity reactions (immediate or delayed), some of which were severe, such as anaphylaxis and angioedema.

Skin and subcutaneous tissue disorders:

Severe skin reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS); psoriasis (including pustular psoriasis and nail psoriasis); nail disorders.

Respiratory, thoracic and mediastinal disorders:

Interstitial lung disease (ILD).

Gastrointestinal disorders:

Stomatitis (such as aphthous or ulcerative), pancreatitis and colitis.

Hepatobiliary disorders:

Drug-induced liver injury (DILI).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of AUBAGIO is important. It allows continued monitoring of the benefit/risk balance of AUBAGIO. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8, or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

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

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

Accelerated elimination procedure: colestyramine and activated charcoal:

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 6 months to reach plasma concentrations less than 0,25 µg/mL. Due to individual variations in medicine clearance, it may take as long as 2 years. An accelerated elimination procedure could be used at any time after discontinuation of AUBAGIO. Elimination can be accelerated by either of the following procedures:

- Administration of colestyramine 8 g every 8 hours for 11 days. If colestyramine 8 g three times a day is not well tolerated, colestyramine 4 g three times a day can be used.
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days.

If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly.

At the end of 11 days, both regimens successfully accelerated teriflunomide elimination, leading to more than 98 % decrease in teriflunomide plasma concentrations.

Use of the accelerated elimination procedure may potentially result in return of disease activity if the patient had been responding to AUBAGIO treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Teriflunomide belongs to the medicine class A 32.16 Others.

Pharmacotherapeutic group: Immunosuppressants, Selective immunosuppressants.

ATC Code: L04AA31.

Teriflunomide is an immunomodulatory medicine with anti-inflammatory properties that reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. As a consequence, teriflunomide blocks the proliferation of stimulated lymphocytes which need de novo synthesis of pyrimidine to expand.

The exact mechanism by which teriflunomide exerts its therapeutic effect in multiple sclerosis (MS) is not fully understood but may include a reduced number of activated lymphocytes in the central nervous system (CNS).
It is likely that teriflunomide diminishes in periphery the numbers of activated lymphocytes available to migrate into the CNS.

Potential to prolong QT interval:
In a placebo-controlled thorough QT study performed in healthy volunteers, 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.

Immune system – effects on immune cell numbers in the blood:
In the placebo-controlled studies, 14 mg teriflunomide 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.

Effect on renal tubular function:
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 oral administration of teriflunomide, with high bioavailability (~ 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 Multiple Sclerosis patients, there is a very slow approach to steady-state concentration (i.e. ~ 100 days (3,5 months) to attain 95 % of steady-state concentrations) and the estimated AUC accumulation ratio is ~ 34-fold.

Distribution:

Teriflunomide is extensively bound to plasma protein (> 99 %) 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 major circulating moiety detected in plasma. The primary biotransformation pathway to minor metabolites of 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 21 days, 60,1 % of the administered dose is excreted via faeces (37,5 %) and urine (22,6 %).

After accelerated elimination procedure with colestyramine, 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 ~ 19 days after repeated doses of 14 mg. After a single IV 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 of teriflunomide from 7 to 14 mg.

Special populations:

Gender and elderly:

Several sources of intrinsic variability were identified in healthy volunteers 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 section 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Hydroxypropylcellulose

Lactose monohydrate

Magnesium stearate

Maize starch

Microcrystalline cellulose

Sodium starch glycolate (Type A).

Tablet coating:

Hypromellose

Indigo carmine aluminium lake (E132)

Macrogol 8000

Talc

Titanium dioxide (E171).

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister stored in the carton/wallet until required for use.

6.5 Nature and contents of container

Thermoformed PA/aluminium/PVC-aluminium blisters inserted in wallets and packed in cartons containing 28 and 84 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBER

47/32.16/0859

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 September 2016

10. DATE OF REVISION OF THE TEXT

20 April 2023