SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

TERIFLUNOMIDE 14 TEVA, 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 TERIFLUNOMIDE 14 TEVA because recommended doses of TERIFLUNOMIDE 14 TEVA and leflunomide result in a similar range of plasma concentrations of TERIFLUNOMIDE 14 TEVA. Obtain transaminase and bilirubin levels within 6 months before initiation of TERIFLUNOMIDE 14 TEVA and monitor ALT levels at least monthly for six months. If medicine induced liver injury is suspected, discontinue TERIFLUNOMIDE 14 TEVA and start accelerated elimination procedure.

Risk of Teratogenicity:

Based on animal data, TERIFLUNOMIDE 14 TEVA may cause major birth defects if used during pregnancy. TERIFLUNOMIDE 14 TEVA is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during TERIFLUNOMIDE 14 TEVA treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

Excipient(s) with known effect: Each film-coated tablet contains 72,25 mg of lactose monohydrate.

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

3. PHARMACEUTICAL FORM:

Film-coated tablets.

Blue, round shaped tablet, debossed with "TV" on one side of the tablet and with "Y12 on the other side of the tablet.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

TERIFLUNOMIDE 14 TEVA 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 TERIFLUNOMIDE 14 TEVA is 14 mg orally once daily.

Special populations:

Elderly population:

TERIFLUNOMIDE 14 TEVA 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 14 TEVA is contraindicated in patients with severe hepatic impairment.

Paediatric population:

The safety and efficacy of TERIFLUNOMIDE 14 TEVA 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. TERIFLUNOMIDE 14 TEVA can be taken with or without food.

4.3. Contraindications:

- Hypersensitivity to teriflunomide or to any of the excipients 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 TERIFLUNOMIDE 14 TEVA with leflunomide is not recommended.
- TERIFLUNOMIDE 14 TEVA is contraindicated for women during pregnancy or women of childbearing potential who are not on reliable contraception during treatment with TERIFLUNOMIDE 14 TEVA and thereafter, as long as its plasma levels are above 0, 02 µg/ml (see **section 4.6**).
- Breast-feeding women (see **section 4.6**).
- Patients with severe immunodeficiency states, e.g. acquired immunodeficiency syndrome (AIDS).
- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia.
- Patients with severe active infection until resolution (see **section 4.4**).

- Patients with severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group.
- Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome

4.4. Special warnings and precautions for use:

Monitoring:

Before treatment:

Before starting treatment with TERIFLUNOMIDE 14 TEVA the following should be assessed:

• Blood pressure

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

• Complete blood cell count including differential white blood cell and platelet count.

During treatment:

During treatment with TERIFLUNOMIDE 14 TEVA the following should be monitored:

• Blood pressure

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

o Liver enzymes should be assessed at least every four weeks during the first 6 months of treatment and regularly thereafter

o Consider additional monitoring when TERIFLUNOMIDE 14 TEVA is given in patients with pre-existing liver disorders, given with other potentially hepatotoxic drugs or as indicated by clinical signs and symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Liver enzymes should be assessed every two weeks during the first 6 months of treatment, and at least every 8 weeks thereafter for at least 2 years from initiation of treatment.

o For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly.

- Complete blood cell counts should be performed based on clinical signs and symptoms (e.g. infections) during treatment.

Accelerated elimination procedure:

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0,02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of TERIFLUNOMIDE 14 TEVA (see **sections 4.6** and **5.2** for procedural details).

Hepatic effects:

Elevations of liver enzymes have been observed in patients receiving TERIFLUNOMIDE 14 TEVA (see **section 4.8**). These elevations occurred mostly within the first 6 months of treatment.

Cases of drug-induced liver injury (DILI) have been observed during treatment with TERIFLUNOMIDE 14 TEVA, sometimes life-threatening. Most cases of DILI occurred with time to onset of several weeks or several months after treatment initiation of TERIFLUNOMIDE 14 TEVA, but DILI can also occur with prolonged use.

The risk for liver enzyme increases and DILI with TERIFLUNOMIDE 14 TEVA might be higher in patients with pre-existing liver disorder, concomitant treatment with other hepatotoxic drugs, and/or consumption of substantial quantities of alcohol. Patients should therefore be closely monitored for signs and symptoms of liver injury.

TERIFLUNOMIDE 14 TEVA should be discontinued and accelerated elimination procedure considered if liver injury is suspected. If elevated liver enzymes (greater than 3 fold ULN) are confirmed, teriflunomide therapy should be discontinued.
In case of treatment discontinuation, liver tests should be pursued until normalisation of transaminase levels.

Hypoproteinaemia:

Since teriflunomide as contained in TERIFLUNOMIDE 14 TEVA, is highly protein bound and as the binding is dependent upon the concentrations of albumin, unbound plasma teriflunomide concentrations are expected to be increased in patients with hypoproteinaemia, e.g. in nephrotic syndrome. TERIFLUNOMIDE 14 TEVA should not be used in patients with conditions of severe hypoproteinaemia.

Blood pressure:

Elevation of blood pressure may occur during treatment with TERIFLUNOMIDE 14 TEVA (see **section 4.8**).
Check blood pressure before start of TERIFLUNOMIDE 14 TEVA and periodically thereafter. Blood pressure elevation should be appropriately managed during treatment with TERIFLUNOMIDE 14 TEVA.

Infections:

Cases of herpes virus infections, including oral herpes and herpes zoster, have been reported with teriflunomide (see **section 4.8**), with some of them being serious, including herpetic meningoencephalitis and herpes dissemination. They may occur at any time during treatment.

Based on the immunomodulatory effect of TERIFLUNOMIDE 14 TEVA, if a patient develops a serious infection, consider suspending treatment with TERIFLUNOMIDE 14 TEVA 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 TERIFLUNOMIDE 14 TEVA to report symptoms of infections to a medical practitioner. Patients with active acute or chronic infections should not start treatment with TERIFLUNOMIDE 14 TEVA until the infection(s) is resolved.

The safety of TERIFLUNOMIDE 14 TEVA in individuals with latent tuberculosis infection is unknown, as tuberculosis screening was not systematically performed in clinical studies. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with TERIFLUNOMIDE 14 TEVA.

Respiratory reactions:

Interstitial lung disease (ILD) as well as cases of pulmonary hypertension have 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 in white blood cell (WBC) count of approximately 15 % (mainly neutrophils and lymphocytes) and in platelet counts of approximately 10 % was observed. The decrease in mean WBC count occurred during the first 6 weeks and WBC count remained low during treatment.
At baseline, a recent blood cell count should be available before the initiation of treatment with TERIFLUNOMIDE 14 TEVA and assessed during TERIFLUNOMIDE 14 TEVA therapy. Further monitoring should be based on signs and symptoms suggestive of infection.

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

In cases of severe haematological reactions, including pancytopenia, TERIFLUNOMIDE 14 TEVA 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).

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

In case of ulcerative stomatitis, TERIFLUNOMIDE 14 TEVA administration should be discontinued. If skin and /or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome), TERIFLUNOMIDE 14 TEVA and any other possibly associated treatment must be discontinued, and an accelerated procedure initiated immediately. In such cases patients should not be re-exposed to TERIFLUNOMIDE 14 TEVA (see **section 4.3**).

New onset of psoriasis (including pustular psoriasis) and worsening of pre-existing psoriasis have been reported during the use of TERIFLUNOMIDE 14 TEVA. Treatment withdrawal and initiation of an accelerated elimination procedure may be considered taking into account patient's disease and medical history.

Peripheral neuropathy:

Cases of peripheral neuropathy have been reported in patients receiving TERIFLUNOMIDE 14 TEVA (see **section 4.8**). Most patients improved after discontinuation of TERIFLUNOMIDE 14 TEVA. However, there was a wide variability in final outcome, i.e. in some patients the neuropathy resolved and some patients had persistent symptoms. If a patient taking TERIFLUNOMIDE 14 TEVA develops a confirmed peripheral neuropathy, consider discontinuing TERIFLUNOMIDE 14 TEVA therapy and performing the accelerated elimination procedure.

Vaccination:

Reports from two clinical studies have shown that vaccinations to inactivated neo-antigen (first vaccination) or recall antigen (re-exposure) were safe and effective during TERIFLUNOMIDE 14 TEVA 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 TERIFLUNOMIDE 14 TEVA 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 14 TEVA 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 TERIFLUNOMIDE 14 TEVA:

Based on the clinical data related to concomitant administration of teriflunomide with interferon beta or with glatiramer acetate, no waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate or when starting interferon beta or glatiramer acetate, after teriflunomide.

Due to the long half-life of natalizumab, concomitant exposure, and thus concomitant immune effects, could occur for up to 2-3 months following discontinuation of natalizumab if TERIFLUNOMIDE 14 TEVA was immediately started. Therefore, caution is required when switching patients from natalizumab to TERIFLUNOMIDE 14 TEVA.

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 TERIFLUNOMIDE 14 TEVA 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 TERIFLUNOMIDE 14 TEVA, during the interval of 5 half-lives (approximately 3,5 months although may be longer in some patients), starting other therapies will result in concomitant exposure to TERIFLUNOMIDE 14 TEVA. 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: Lactose:

TERIFLUNOMIDE 14 TEVA contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TERIFLUNOMIDE 14 TEVA.

4.5. Interaction with other medicines and other forms of interaction:

Pharmacokinetic interactions of other substances on TERIFLUNOMIDE 14 TEVA**:**

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.

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 14 TEVA (70 mg single dose) resulted in an approximately 40 % decrease in TERIFLUNOMIDE 14 TEVA 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 the treatment with TERIFLUNOMIDE 14 TEVA.

Cholestyramine or activated charcoal:

It is recommended that patients receiving TERIFLUNOMIDE 14 TEVA 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 14 TEVA.

Pharmacokinetic interactions of TERIFLUNOMIDE 14 TEVA on other substances

Effect of TERIFLUNOMIDE 14 TEVA 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 14 TEVA, suggesting that TERIFLUNOMIDE 14 TEVA 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 **TERIFLUNOMIDE 14 TEVA**.

Effect of TERIFLUNOMIDE 14 TEVA 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 14 TEVA. While this interaction of TERIFLUNOMIDE 14 TEVA is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment used in combination with TERIFLUNOMIDE 14 TEVA.

Effect of TERIFLUNOMIDE 14 TEVA on CYP1A2 substrate: caffeine

Repeated doses of TERIFLUNOMIDE 14 TEVA decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18 % and 55 %, respectively, suggesting that TERIFLUNOMIDE 14 TEVA 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 TERIFLUNOMIDE 14 TEVA, as it could lead to the reduction of the efficacy of these medicines.

Effect of TERIFLUNOMIDE 14 TEVA on warfarin:

Repeated doses of TERIFLUNOMIDE 14 TEVA had no effect on the pharmacokinetics of S-warfarin, indicating that TERIFLUNOMIDE 14 TEVA is not an inhibitor or an inducer of CYP2C9. However, a 25 % decrease in peak international normalised ratio (INR) was observed when TERIFLUNOMIDE 14 TEVA was co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered with TERIFLUNOMIDE 14 TEVA, close INR follow-up and monitoring is recommended.

*Effect of **TERIFLUNOMIDE 14 TEVA** 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 14 TEVA, suggesting that TERIFLUNOMIDE 14 TEVA is an inhibitor of OAT3 *in vivo*. Therefore, when

TERIFLUNOMIDE 14 TEVA is co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, and zidovudine, caution is recommended.

Effect of TERIFLUNOMIDE 14 TEVA *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 14 TEVA. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. For rosuvastatin, a dose reduction by 50 % is recommended for co-administration with TERIFLUNOMIDE 14 TEVA. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration of TERIFLUNOMIDE 14 TEVA 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 TERIFLUNOMIDE 14 TEVA treatment is considered low; however, patients should be advised to use barrier contraception.

Use in females:

TERIFLUNOMIDE 14 TEVA is contraindicated in women of childbearing potential not using reliable contraceptives.

Women of childbearing potential must use effective contraception during treatment and after treatment as long as TERIFLUNOMIDE 14 TEVA 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:

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

TERIFLUNOMIDE 14 TEVA may cause serious birth defects when administered during pregnancy. TERIFLUNOMIDE 14 TEVA is contraindicated in pregnancy (see **section 4.3**).

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the medical practitioner immediately for pregnancy testing, and if positive, the medical practitioner and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of TERIFLUNOMIDE 14 TEVA, by instituting the accelerated elimination procedure described below, at the first delay of menses, may decrease the risk to the foetus.

For women receiving TERIFLUNOMIDE 14 TEVA treatment, who wish to become pregnant, the medicine should be stopped, and an accelerated elimination procedure is recommended in order to more rapidly achieve concentration below 0,02 mg/l (see **sections 4.4** and **4.9**).

If an accelerated elimination procedure is not used, TERIFLUNOMIDE 14 TEVA plasma levels can be expected to be above 0,02 mg/l for an average of 8 months, however, in some patients it may take up to 2 years to reach plasma concentration

below 0,02 mg/l. Therefore, TERIFLUNOMIDE 14 TEVA plasma concentrations should be measured before a woman begins to attempt to become pregnant. Once TERIFLUNOMIDE 14 TEVA plasma concentration is determined to be below 0,02 mg/l, the plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0,02 mg/l, no risk to the foetus is to be expected.

Accelerated elimination procedure:

After stopping treatment with TERIFLUNOMIDE 14 TEVA:

- cholestyramine 8 g is administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated,
- alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days

However, also following either of the accelerated elimination procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0,02 mg/l and fertilisation is required.

Both cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the accelerated elimination procedure with cholestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Breastfeeding:

Animal studies have shown excretion of TERIFLUNOMIDE 14 TEVA in milk.

TERIFLUNOMIDE 14 TEVA is contraindicated during breastfeeding (see **section 4.3**).

Fertility:

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

4.7. Effects on ability to drive and use machines:

TERIFLUNOMIDE 14 TEVA has no or negligible influence on the ability to drive and use machines.

However, 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 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, herpes virus infection, oral herpes, tooth infection, laryngitis, tinea pedis
Frequency not known:	Severe infections including sepsis[a]
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
Less frequent:	Peripheral neuropathy, hyperaesthesia, neuralgia
Cardiac disorders	
Frequent:	Palpitations
Vascular disorders	
Frequent:	Hypertension[b]
Respiratory, thoracic and mediastinal disorders	
Frequency not known:	Interstitial lung disease, pulmonary hypertension
Gastrointestinal disorders	
Frequent:	Diarrhoea, nausea, upper abdominal pain, vomiting, toothache
Less frequent :	Colitis
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, Drug-induced liver injury (DILI)
Skin and subcutaneous tissue disorders	
Frequent:	Alopecia, rash, acne
Less frequent:	Nail disorders, severe skin reactions, psoriasis (including pustular)
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. 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 providers 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 **TERIFLUNOMIDE 14 TEVA** overdose or intoxication in humans.

Management:

In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination. The recommended elimination procedure is cholestyramine 8 g three times a day for 11 days. If this is not well tolerated, cholestyramine 4 g three times a day for 11 days can be used. Alternatively, when cholestyramine is not available, activated charcoal 50 g twice a day for 11 days may also be used. In addition, if required for tolerability reasons, administration of cholestyramine or activated charcoal does not need to occur on consecutive days (see **section 5.2**).

5. PHARMACOLOGICAL PROPERTIES:

5.1. Pharmacodynamic properties:

Pharmacotherapeutic group: Immunosuppressants, Selective immunosuppressants,

ATC Code: L04AA31

Mechanism of action:

Teriflunomide is an immunomodulatory 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 activated lymphocytes in the central nervous system (CNS).

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 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 109/l, which occurred over the first 3 months of treatment and levels were maintained until the end of the treatment.

Potential to prolong the QT interval:

In a placebo-controlled thorough QT study performed in healthy subjects, teriflunomide at mean steady-state concentrations did not show any potential for prolonging the QTcF interval compared with placebo: the largest time matched mean difference between teriflunomide and placebo was 3,45 ms with the upper bound of the 90 % CI being 6,45 ms.
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 accelerated 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 t1/2z was approximately 19 days after repeated doses of 14 mg. After a single intravenous administration, the total body clearance of teriflunomide is 30,5 ml/h.

Linearity/non-linearity:

Systemic exposure increases in a dose proportional manner after oral administration teriflunomide from 7 to 14 mg.

Special Populations:

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.

6. PHARMACEUTICAL PARTICULARS:

6.1. List of excipients:

Tablet core:

Colloidal silicone dioxide

Hydroxypropyl cellulose

Lactose monohydrate

Microcrystalline cellulose

Sodium starch glycolate

Sodium stearyl fumarate

Starch

Tablet coating:

Opadry 03F205013 Blue

Hypromellose 2910

Indigo carmine aluminium lake/FD&C blue #2

Macrogol/PEG

Talc

Titanium dioxide

6.2. Incompatibilities:

Not applicable

6.3. Shelf life:

36 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:

Silver Alu-Alu blisters inserted in wallets and packed in cartons containing 14, 28, 84 (3 wallets of 28) and 98 (7 wallets of 14) film-coated tablets.

7 film-coated tablets per blister.

Each wallet is placed in a protective sleeve.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product:

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

1st Floor, Building 3 Maxwell Office Park

Magwa Cresent West, Waterfall City

Midrand

8. REGISTRATION NUMBER:

54/32.16/0737

9. DATE OF FIRST AUTHORISATION:

17 May 2022

10. DATE OF REVISION OF TEXT

07 February 2025