Teragio®

Teriflunomide

FORMS AND PRESENTATION
Teragio®: Film Coated Tablets; Box of 28 or 30.

COMPOSITION
Teragio®: Each film coated tablet contains 14 mg of teriflunomide.
Excipients: Lactose monohydrate, maize starch, sodium starch glycolate, hydroxypropyl cellulose, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide, talc, polyethylene glycol, FD&C Blue.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Selective immunosuppressants,
ATC Code: L04AA31.
Mechanism of action
Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. As a consequence teriflunomide reduces the proliferation of dividing cells that need de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.
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.
Distribution
Teriflunomide is extensively bound to plasma protein (>99%), probably albumin and is mainly distributed in plasma. The volume of distribution is 11 l after a single intravenous (IV) administration. However, this is most likely an underestimation since extensive organ distribution was observed in rats.
Biotransformation
Teriflunomide is moderately metabolized and is the only component detected in plasma. The primary biotransformation pathway for teriflunomide is hydrolysis with oxidation being a minor pathway. Secondary pathways involve oxidation, N-acetylation and sulfate conjugation.
Elimination
Teriflunomide is excreted in the gastrointestinal tract mainly through the bile as unchanged medicinal product and most likely by direct secretion. Teriflunomide is a substrate of the efflux transporter BCRP, which could be involved in direct secretion. Over 21 days, 60.1% of the administered dose is excreted via feces (37.5%) and urine (22.6%). After the rapid elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in feces).

INDICATIONS
Teragio® is indicated for the treatment of adult and pediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS).

CONTRAINDICATIONS
• Hypersensitivity to the active substance or to any of the excipients listed.
• Patients with severe hepatic impairment (Child-Pugh class C).
• Pregnant women or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/l. Pregnancy must be excluded before start of treatment.
• Breast-feeding women.
• Patients with severe immunodeficiency states, e.g. AIDS.
• Patients with significantly impaired bone marrow function or significant anemia, leucopenia, neutropenia or thrombocytopenia.
• Patients with severe active infection until resolution.
• Patients with severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group.
• Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.

PRECAUTIONS
Monitoring
Before starting treatment with teriflunomide 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 with teriflunomide the following should be monitored:
• Blood pressure: Check periodically
• Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)
– Liver enzymes should be assessed at least every four weeks during the first 6 months of treatment and regularly thereafter.
– Consider additional monitoring when teriflunomide 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.
– 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.
Hepatic effects
Elevations of liver enzymes have been observed in patients receiving teriflunomide. 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, sometimes life-threatening. Most cases of DILI occurred with time to onset of several weeks or several months after treatment initiation of teriflunomide, but DILI can also occur with prolonged use.
The risk for liver enzyme increases and DILI with teriflunomide 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 therapy 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 normalization of transaminase levels.
Hypoproteinaemia
Since teriflunomide is highly protein bound and as the binding is dependent upon the concentrations of albumin, unbound plasma teriflunomide concentrations are expected to be increased in patients with hypoproteinaemia, e.g. in nephrotic syndrome. Teriflunomide should not be used in patients with conditions of severe hypoproteinaemia.
Blood pressure
Elevation of blood pressure may occur during treatment with teriflunomide. Blood pressure must be checked before the start of teriflunomide treatment and periodically thereafter. Blood pressure elevation should be appropriately managed before and during treatment with teriflunomide.
Infections
Initiation of treatment with teriflunomide should be delayed in patients with severe active infection until resolution.
However, based on the immunomodulatory effect of teriflunomide tablets, if a patient develops a serious infection, suspending treatment with teriflunomide tablets should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Due to the prolonged half-life, accelerated elimination with cholestyramine or charcoal may be considered.
Patients with active acute or chronic infections should not start treatment with teriflunomide until the infection(s) is resolved.
For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with teriflunomide.
Respiratory reactions
Interstitial lung disease (ILD) has been reported with teriflunomide in the postmarketing 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 dyspnea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. If discontinuation of the drug is necessary, consider initiation of an accelerated elimination procedure.
Hematological effects
A mean decrease less than 15% from baseline affecting white blood cell count has been observed. As a precaution, a recent complete blood cell count, including differential white blood cell count and platelets, should be available before the initiation of treatment with teriflunomide and the complete blood cell count should be assessed during teriflunomide therapy as indicated by clinical signs and symptoms (e.g., infections).
In patients with pre-existing anemia, leucopenia, and /or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of haematological disorders is increased. If such effects occur, the accelerated elimination procedure to reduce plasma levels of teriflunomide should be considered.
In cases of severe haematological reactions, including pancytopenia, teriflunomide and any concomitant myelosuppressive treatment must be discontinued and a teriflunomide accelerated elimination procedure should be considered.
Skin reactions
In case of ulcerative stomatitis, teriflunomide administration should be discontinued. If skin and /or mucosal reactions are observed which raise the suspicion of severe generalized major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome), teriflunomide and any other possibly associated treatment must be discontinued, and an accelerated procedure initiated immediately. In such cases patients should not be re-exposed to teriflunomide.
Peripheral neuropathy
Cases of peripheral neuropathy have been reported in patients receiving teriflunomide. Most patients improved after discontinuation of teriflunomide. 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 develops a confirmed peripheral neuropathy, consider discontinuing teriflunomide therapy and performing the accelerated elimination procedure.
Vaccination
The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.
Immunosuppressive or immunomodulating therapies
As leflunomide is the parent compound of teriflunomide, co-administration of teriflunomide with leflunomide is not recommended.
Co-administration with antineoplastic or immunosuppressive therapies used for treatment of MS has not been evaluated. The long term safety of these combinations in the treatment of multiple sclerosis has not been established.
Switching to or from teriflunomide
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 was immediately started. Therefore, caution is required when switching patients from natalizumab to teriflunomide.
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 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, 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. This may lead to an additive effect on the immune system and caution is, therefore, indicated.
Paediatric population
Pancreatitis
In the paediatric clinical trial, cases of pancreatitis, some acute, have been observed in patients receiving teriflunomide. Clinical symptoms included abdominal pain, nausea and/or vomiting. Serum amylase and lipase were elevated in these patients. The time to onset ranged from a few months up to three years. Patients should be informed of the characteristic symptoms of pancreatitis. If pancreatitis is suspected, pancreatic enzymes and related laboratory parameters should be obtained. If pancreatitis is confirmed, teriflunomide should be discontinued and an accelerated elimination procedure should be initiated.
Lactose
Since teriflunomide tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.
Interference with determination of ionized calcium levels
The measurement of ionized calcium levels might show falsely decreased values under treatment with leflunomide and/or teriflunomide (the active metabolite of leflunomide) depending on the type of ionized calcium analyser used (e.g. blood gas analyser). Therefore, the plausibility of observed decreased ionized 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.
Effects on ability to drive and use machines
Teriflunomide 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 cars and using machines.

FERTILITY, PREGNANCY AND LACTATION

Use in males

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

Pregnancy

Studies in animals have shown reproductive toxicity.

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

Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. During this period women should discuss any plans to stop or change contraception with the treating physician.

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing, and if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of teriflunomide, by instituting the accelerated elimination procedure described below, at the first delay of menses, may decrease the risk to the foetus. For women receiving teriflunomide treatment, who wish to become pregnant, the medicine should be stopped and an accelerated elimination procedure is recommended in order to more rapidly achieve concentration below 0.02 mg/l (see below).

If an accelerated elimination procedure is not used, teriflunomide plasma levels can be expected to be above 0.02 mg/l for an average of 8 months, however, in some patients it may take up to 2 years to reach plasma concentration below 0.02 mg/l. Therefore, teriflunomide plasma concentrations should be measured before a woman begins to attempt to become pregnant. Once the teriflunomide plasma concentration is determined to be below 0.02 mg/l, the plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l, no risk to the foetus is to be expected.

Accelerated elimination procedure

After stopping treatment with teriflunomide:

• cholestyramine 8 g is administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated,

• alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days.

However, also following either of the accelerated elimination procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation is required.

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

Breast-feeding

Animal studies have shown excretion of teriflunomide in breast milk. Breast-feeding women must, therefore, not receive teriflunomide.

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.

DRUG INTERACTIONS

Pharmacokinetic interactions of other substances on 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] with teriflunomide (70 mg single dose) resulted in an approximately 40% decrease in teriflunomide exposure. Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin and St John's Wort should be used with caution during the treatment with teriflunomide.

Cholestyramine or activated charcoal

It is recommended that patients receiving teriflunomide are not treated with cholestyramine or activated charcoal because this leads to a rapid and significant decrease in plasma concentration unless an accelerated elimination is desired. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of teriflunomide.

Pharmacokinetic interactions of teriflunomide on other substances

Effect of teriflunomide on CYP2C8 substrate: repaglinide

There was an increase in mean repaglinide Cmax and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo. Therefore, medicinal products metabolized by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during treatment with teriflunomide.

Effect of teriflunomide on oral contraceptive: 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel

There was an increase in mean ethinylestradiol C_{max} and AUC_{0-24} (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC_{0-24} (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide. While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment used in combination with teriflunomide.

Effect of teriflunomide on CYP1A2 substrate: caffeine

Repeated doses of teriflunomide decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 in vivo. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetin, alosetron, theophylline and tizanidine) should be used with caution during treatment with teriflunomide, as it could lead to the reduction of the efficacy of these products.

Effect of teriflunomide on warfarin

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

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

There was an increase in mean cefaclor 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 teriflunomide is coadministered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.

Effect of teriflunomide on BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates:

There was an increase in mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively), following repeated doses of teriflunomide. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. For rosuvastatin, a dose reduction by 50% is recommended for coadministration with teriflunomide. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration of teriflunomide should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

ADVERSE EFFECTS

The most commonly reported adverse reactions in the teriflunomide treated patients were: headache, diarrhea, increased ALT, nausea, and alopecia. In general, headache, diarrhea, nausea and alopecia, were mild to moderate, transient and infrequently led to treatment discontinuation.

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

• Infections and infestations: Influenza, Upper respiratory tract infection, Urinary tract infection, Bronchitis, Sinusitis, Pharyngitis, Cystitis, Gastroenteritis viral, Herpes virus infections, Tooth infection, Laryngitis, Tinea pedis (common); Severe infections including sepsis (not known).

• Blood and lymphatic system disorders: Neutropenia, Anaemia (common); Mild thrombocytopenia (platelets <100G/l) (uncommon).

• Immune system disorders: Mild allergic reactions (common); Hyper-sensitivity reactions (immediate or delayed) including anaphylaxis and angioedema (uncommon).

• Psychiatric disorders: Anxiety (common).

• Nervous system disorders: Headache (very common); Paraesthesia, Sciatica, Carpal tunnel syndrome (common); Hyperaesthesia, Neuralgia, Peripheral neuropathy (uncommon).

• Cardiac disorders: Palpitations (common).

• Vascular disorders: Hypertension (common).

• Respiratory, thoracic and mediastinal disorders: Interstitial lung disease (uncommon), pulmonary hypertension (not known).

• Gastrointestinal disorders: Diarrhoea, Nausea (very common); Pancreatitis; upper Abdominal pain , Vomiting, Toothache (common); Stomatitis Colitis (uncommon).

• Hepatobiliary disorders: Alanine aminotransferase (ALT) increase (very common); Gamma-glutamyltransferase (GGT) increase, Aspartate aminotransferase increase (common); Acute hepatitis (rare), Drug-induced liver injury (DILI) (not known).

• Skin and subcutaneous tissue disorders: Alopecia (very common); Rash, Acne (common); severe skin reactions, Nail disorders; Psoriasis (including pustular) (uncommon).

• Musculoskeletal and connective tissue disorders: Musculoskeletal pain, Myalgia, Arthralgia (common).

• Metabolism and nutrition disorders: Dyslipidaemia (uncommon).

• Renal and urinary disorders: Pollakiuria (common).

• Reproductive system and breast disorders: Menorrhagia (common).

• General disorders and administration site conditions: Pain, Asthenia (common).

• Investigations: Weight decrease, Neutrophil count decrease, White blood cell count decrease, Blood creatine phosphokinase increased (common).

• Injury, poisoning and procedural complications: Post-traumatic pain (uncommon).

DOSAGE AND ADMINISTRATION

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

Posology

Adults

In adults, the recommended dose of Teragio® is 14 mg once daily.

Paediatric population (10 years and older)

In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:

- Paediatric patients with body weight >40 kg: 14 mg once daily.
- Paediatric patients with body weight ≤40 kg: 7 mg once daily.

Paediatric patients who reach a stable body weight above 40 kg should be switched to 14 mg once daily.

Film-coated tablets can be taken with or without food.

Special populations

Elderly population

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

Renal impairment

No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis.

Patients with severe renal impairment undergoing dialysis were not evaluated. Teriflunomide is contraindicated in this population

Hepatic impairment

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

Paediatric population

The safety and efficacy of Teragio® in children aged less than 10 years has not yet been established.

Method of administration

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

OVERDOSAGE

Symptoms

There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily was administered up to 14 days in healthy subjects. The adverse reactions were consistent with the safety profile for teriflunomide in MS patients.

Management

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

STORAGE CONDITIONS

Store below 30˚C.

Keep in original pack in intact conditions.

Date of Revision: June 2025.

Marketing Authorization Holder
Benta S.A.L - Lebanon

Manufacturer
Manufactured by Alembic Pharmaceuticals Limited, India
For Benta S.A.L. - Lebanon

BPI

PI248/3