

เอกสารกำกับยาภาษาอังกฤษ

AUBAGIO (14 mg)

NAME OF THE MEDICINAL PRODUCT

AUBAGIO 14 mg film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 14 mg of teriflunomide.

Excipient with known effect: Each tablet contains 72 mg of lactose (as monohydrate).

For the full list of excipients, (see List of excipients)

PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side ('14') and engraved with a corporate logo on the other side.

CLINICAL PARTICULARS

Therapeutic indications

AUBAGIO (teriflunomide) is indicated as monotherapy for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Posology and method of administration

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

Posology

The recommended dose of AUBAGIO is 14 mg once daily.

Special populations

Elderly population

AUBAGIO 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 (see Contraindications).

Hepatic impairment

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

Paediatric population

The safety and efficacy of AUBAGIO in children aged from 10 to less than 18 years has not yet been established. There is no relevant use of teriflunomide in children aged from birth to less than 10 years for the treatment of multiple sclerosis.

No data are available.

Method of administration

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

Contraindications

Hypersensitivity to the teriflunomide, leflunomide (parent compound) or to any of the excipients listed in List of excipients.

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 (see Fertility, pregnancy and lactation).

Pregnancy must be excluded before start of treatment (see Fertility, pregnancy and lactation).

Breast-feeding women (see Fertility, pregnancy and lactation).

Patients with severe immunodeficiency states, e.g. AIDS.

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

Patients with severe active infection until resolution (see Special warnings and precautions for use).

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.

Special warnings and precautions for use

Monitoring

Before treatment

Before starting treatment with teriflunomide the following should be assessed:

- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell count including differential white blood cell and platelet count.

During treatment

During treatment with teriflunomide the following should be monitored:

- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell counts should be performed based on signs and symptoms (e.g. infections) during treatment.

Accelerated elimination procedure

Teriflunomide is eliminated slowly from the plasma. When desired, an accelerated elimination procedure can be used. 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 (see Fertility, pregnancy and lactation and Pharmacokinetic properties for procedural details).

Hepatic effects

Elevations of liver enzymes have been observed in patients receiving teriflunomide (see Undesirable effects). These elevations occurred mostly within the first 6 months of treatment.

Serum transaminase and bilirubin levels should be assessed within 6 months before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting,

abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Consider monitoring when AUBAGIO is given with other potentially hepatotoxic drugs. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. If liver injury is suspected to be AUBAGIO-induced, discontinue teriflunomide and start an accelerated elimination procedure and monitor liver tests weekly until normalized. Consider discontinuing teriflunomide therapy if elevated serum transaminase (greater than 3-fold ULN) are confirmed. Patients with preexisting liver disease may be at increased risk of developing elevated liver enzymes when taking teriflunomide and should be closely monitored for signals of liver disease. If teriflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of teriflunomide therapy may be considered.

The medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

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 (see Undesirable effects). 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.

In placebo-controlled studies, no increase in serious infections was observed with teriflunomide (see Undesirable effect). However, based on the immunomodulatory effect of AUBAGIO, if a patient develops a serious infection, suspending treatment with AUBAGIO 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 receiving AUBAGIO should be instructed to report symptoms of infections to a physician. 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. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with AUBAGIO.

Respiratory reactions

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

Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during treatment with leflunomide the parent compound. 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 dyspnea, with or without associated fever, 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.

Haematological effects

A mean decrease in white blood cell (WBC) count of approximately 15% (mainly neutrophils and lymphocytes) and in platelet count of approximately 10% was observed in placebo-controlled trials with 7 mg and 14 mg of 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 $< 1.5 \times 10^9/L$ was observed in 12% and 16% of patients on AUBAGIO 7 mg and 14 mg, respectively, compared with 7% of patients on placebo; lymphocyte count $< 0.8 \times 10^9/L$ was observed in 10% and 12% of patients on AUBAGIO 7 mg and 14 mg, respectively, 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.

Skin reactions

No cases of severe skin reactions have been reported with teriflunomide in the clinical trials. In patients treated with leflunomide, the parent compound, very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported.

In 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 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 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 (see Contraindications).

Peripheral neuropathy

Cases of peripheral neuropathy have been reported in patients receiving AUBAGIO (see Undesirable effects). 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.

Vaccination

Two clinical studies have shown that vaccinations to inactivated neoantigen (first vaccination), or recall antigen (reexposure) were safe and effective during AUBAGIO treatment. 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. Safety studies, in which teriflunomide was concomitantly administered with interferon beta or with glatiramer acetate for up to one year did not reveal any specific safety concerns, 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 AUBAGIO

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 AUBAGIO was immediately started.

Therefore, caution is required when switching patients from natalizumab to AUBAGIO.

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

Lactose

Since AUBAGIO 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.

Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions of other substances on teriflunomide

The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway.

Potent cytochrome P450 (CYP) and transporter inducers

Co-administration of repeated doses (600 mg once daily for 22 days) of rifampicin (a CYP2B6, 2C8, 2C9, 2C19, 3A inducer), as well as an inducer of the efflux transporters P-glycoprotein [P-gp] and breast cancer resistant protein [BCRP] with teriflunomide (70 mg single dose) resulted in an approximately 40% decrease in teriflunomide exposure. Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, 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 C_{max} and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 *in vivo*. Therefore, medicinal products metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during treatment with 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, consideration should be given to the type or dose of oral contraceptives 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 duloxetine, 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.

Fertility, pregnancy and lactation

Use in males

The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low (see Preclinical safety data).

Pregnancy

There are limited amount of data from the use of teriflunomide in pregnant women. Studies in animals have shown reproductive toxicity (see Preclinical safety data).

Teriflunomide may increase the risk of fetal death or teratogenic effects when administered to pregnant women. Teriflunomide is contraindicated in pregnancy (see Contraindications).

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, minimal risk to the foetus is to be expected (based on available animal data).

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 (see Preclinical safety data). Although human data are lacking, no effect on male and female fertility is anticipated.

Effects on ability to drive and use machines

AUBAGIO 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.

Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common ≥ 10 %; Common ≥ 1 and < 10 %; Uncommon ≥ 0.1 and < 1 %; Rare ≥ 0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).

The most frequent adverse reactions for AUBAGIO (incidence $\geq 10\%$ and $\geq 2\%$ greater than placebo) in the placebo-controlled studies were headache, diarrhea, nausea, alopecia, ALT increased.

Clinical Trial Experience

A total of 2,047 patients on teriflunomide (7 or 14 mg once daily) and 997 on placebo constituted the safety population in the pooled analysis of placebo controlled studies in patients with relapsing forms of MS (RMS).

Adverse Reactions in placebo controlled studies occurring in $\geq 1\%$ of patients, and reported for teriflunomide 7 mg or 14 mg at $\geq 1\%$ higher rate than for placebo)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=997)	Teriflunomide	
		7 mg (N=1045)	14 mg (N=1002)
INFECTIONS AND INFESTATIONS			
Influenza	70 (7.0%)	71 (6.8%)	88 (8.8%)
Sinusitis	42 (4.2%)	50 (4.8%)	53 (5.3%)
Gastroenteritis viral	11 (1.1%)	18 (1.7%)	24 (2.4%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Neutropenia	19 (1.9%)	44 (4.2%)	59 (5.9%)
NERVOUS SYSTEM DISORDERS			
Headache	150 (15.0%)	186 (17.8%)	157 (15.7%)
Paraesthesia	67 (6.7%)	79 (7.6%)	88 (8.8%)
CARDIAC DISORDERS			
Palpitations	10 (1.0%)	21 (2.0%)	12 (1.2%)
VASCULAR DISORDERS			
Hypertension	18 (1.8%)	32 (3.1%)	43 (4.3%)
GASTROINTESTINAL DISORDERS			
Diarrhoea	75 (7.5%)	137 (13.1%)	136 (13.6%)
Nausea	72 (7.2%)	84 (8.0%)	107 (10.7%)
Abdominal pain upper	36 (3.6%)	51 (4.9%)	50 (5.0%)
Toothache	18 (1.8%)	31 (3.0%)	29 (2.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia	50 (5.0%)	102 (9.8%)	135 (13.5%)
Rash	32 (3.2%)	43 (4.1%)	45 (4.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia	52 (5.2%)	80 (7.7%)	58 (5.8%)
Musculoskeletal pain	21 (2.1%)	35 (3.3%)	33 (3.3%)
Myalgia	15 (1.5%)	30 (2.9%)	24 (2.4%)

REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Menorrhagia	4 (0.4%)	8 (0.8%)	16 (1.6%)
INVESTIGATIONS			
Alanine aminotransferase increased	89 (8.9%)	136 (13.0%)	150 (15.0%)
Aspartate aminotransferase increased	17 (1.7%)	29 (2.8%)	34 (3.4%)
Gamma-glutamyltransferase increased	9 (0.9%)	24 (2.3%)	24 (2.4%)
Weight decreased	8 (0.8%)	19 (1.8%)	24 (2.4%)
Neutrophil count decreased	11 (1.1%)	23 (2.2%)	22 (2.2%)
Blood creatine phosphokinase increased	7 (0.7%)	21 (2.0%)	16 (1.6%)
White blood cell count decreased	4 (0.4%)	21 (2.0%)	13 (1.3%)

Peripheral neuropathy

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), was reported more frequently in patients taking teriflunomide than in patients taking placebo. In the pivotal, placebo-controlled studies, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.4% (13 patients) and 1.9% (16 patients) on 7 mg and 14 mg of AUBAGIO, respectively, compared with 0.4% on placebo (4 patients). Treatment was discontinued in 8 patients with confirmed peripheral neuropathy (3 on teriflunomide 7 mg and 5 on teriflunomide 14 mg). Recovery following treatment discontinuation was reported in the 4 of these patients. Not all cases of peripheral neuropathy resolved with continued treatment.

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

There does not appear to be an increased risk of malignancy with teriflunomide in the clinical trial experience. The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some other agents that affect the immune system (class effect).

Post-marketing Experience

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 and Stevens-Johnson syndrome
 - Psoriasis (including pustular psoriasis)
- Respiratory, thoracic and mediastinal disorders

- Interstitial Lung Disease (ILD)
- Gastrointestinal Disorders
 - Stomatitis (such as aphthous or ulcerative)
 - Pancreatitis

Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Overdose

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 (see Pharmacokinetic properties).

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 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 MS is not fully understood, but may include reduced number of activated lymphocytes in central nervous system (CNS). 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 $0.3 \times 10^9/l$, which occurred over the first 3 months of treatment and levels were maintained until the end of the treatment.

Potential to prolong the QT interval

In a placebo-controlled thorough QT study performed in healthy subjects, teriflunomide at mean steady-state concentrations did not show any potential for prolonging the QTcF interval compared with placebo: the largest time matched mean difference between teriflunomide and placebo was 3.45 ms with the upper bound of the 90% CI being 6.45 ms.

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 10-15% 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.

Clinical efficacy and safety

The efficacy of AUBAGIO was demonstrated in two placebo controlled studies, the TEMSO and the TOWER study, that evaluated once daily doses of teriflunomide 7 mg and 14 mg in patients with RMS.

A total of 1088 patients with RMS were randomised in TEMSO to receive 7 mg (n=366) or 14 mg (n=359) of teriflunomide or placebo (n= 363) for 108 weeks duration. All patients had a definite diagnosis of MS (based on McDonald criteria (2001)), exhibited a relapsing clinical course, with or without progression, and experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ≤ 5.5 .

The mean age of the study population was 37.9 years. The majority of patients had relapsing–remitting multiple sclerosis (91.5%), but a subgroup of patients had secondary progressive (4.7%) or progressive relapsing multiple sclerosis (3.9%). The mean number of relapses within the year before study inclusion was 1.4 with 36.2% of patients having gadolinium-enhancing lesions at baseline. The median EDSS score at baseline was 2.50; 249 patients (22.9%) had an EDSS score > 3.5 at baseline. The mean duration of disease, since first symptoms, was 8.7 years. A majority of patients (73%) had not received disease-modifying therapy during the 2 years before study entry. The study results are shown in Table 1.

Long term follow-up results from TEMSO long term extension safety study (overall median treatment duration approximately 5 years, maximum treatment duration approximately 8.5 years) did not present any new or unexpected safety findings.

A total of 1169 patients with RMS were randomised in TOWER to receive 7 mg (n=408) or 14 mg (n=372) of teriflunomide or placebo (n= 389) for a variable treatment duration ending at 48 weeks after last patient randomised. All patients had a definite diagnosis of MS (based on McDonald criteria (2005)), exhibited a relapsing clinical course, with or without progression, and experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ≤ 5.5 .

The mean age of the study population was 37.9 years. The majority of patients had relapsing–remitting multiple sclerosis (97.5%), but a subgroup of patients had secondary progressive (0.8%) or progressive relapsing multiple sclerosis (1.7%). The mean number of relapses within the year before study inclusion was 1.4. Gadolinium-enhancing lesions at baseline: no data. The median EDSS score at baseline was 2.50; 298 patients (25.5%) had an EDSS score > 3.5 at baseline. The mean duration of disease, since first symptoms, was 8.0 years. A majority of patients (67.2%) had not received disease-modifying therapy during the 2 years before study entry. The study results are shown in Table 1.

Table 1 – Main Results (for the approved dose, ITT population)

	TEMSO-study		TOWER-study	
	Teriflunomide 14 mg	Placebo	Teriflunomide 14 mg	Placebo
N	358	363	370	388
Clinical outcomes				
Annualised relapse rate	0.37	0.54	0.32	0.50
<i>Risk different (CI_{95%})</i>	-0.17 (-0.26, -0.08)***		-0.18 (-0.27, -0.09)***	
Relapse-free week 108	56.5%	45.6%	57.1%	46.8%
Hazard ratio (CI _{95%})	0.72 (0.58, 0.89)**		0.63 (0.50, 0.79)****	
3-month Sustained Disability Progression	20.2%	27.3%	15.8%	19.7%
<i>Week 108 Hazard ratio (CI_{95%})</i>	0.70 (0.51, 0.97)*		0.68 (0.47, 1.00)*	
6-month Sustained Disability Progression	13.8%	18.7%	11.7%	11.9%
<i>Week 108 Hazard ratio (CI_{95%})</i>	0.75 (0.50, 1.11)		0.84 (0.53, 1.33)	
MRI endpoints				
Change in BOD week 108 ⁽¹⁾	0.72	2.21		
<i>Change relative to placebo</i>	67%***			
Mean Number of Gd-enhancing lesions at week 108	0.38	1.18		
<i>Change relative to placebo (CI_{95%})</i>	-0.80 (-1.20, -0.39)****		Not Measured	
Number of unique active lesions/scan	0.75	2.46		
<i>Change relative to placebo (CI_{95%})</i>	69%, (59%; 77%)****			

**** p<0.0001 *** p<0.001 ** p<0.01 * p<0.05 compared to placebo

(1) BOD: burden of disease: total lesion volume (T2 and T1 hypointense) in ml

However, the studies show that the dose of teriflunomide 14 mg/day is considered to provide a better benefit/risk ratio than the dose of teriflunomide 7 mg/day. The dose of teriflunomide 14 mg/day was found to have greater activity on several endpoints (MRI outcomes with fewer T1-Gd lesions per scan, relapses with sequelae and relapses leading to hospitalisation or emergency medical facility, disability) compared to teriflunomide 7 mg/day.

On the safety/tolerability side, there was no indication of a significant increased safety risk with the dose of teriflunomide 14 mg as compared to 7 mg and only modest differences between the 2 doses were observed in the frequency of AEs, which were generally of mild to moderate intensity and infrequently led to treatment discontinuation with either dose.

Efficacy in patients with high disease activity:

A consistent treatment effect on relapses and time to 3-month sustained disability progression in a subgroup of patients in TEMSO (n= 127) with high disease activity was observed. Due to the design of the study, high disease activity was defined as 2 or more relapses in one year, and with one or more Gd-enhancing lesion on brain MRI. No similar subgroup analysis was performed in TOWER as no MRI data were obtained.

No data are available in patients who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or patients having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years.

TOPIC was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg for up to 108 weeks in patients with first clinical demyelinating event (mean age 32.1 years). The primary endpoint was time to a second clinical episode (relapse). A total of 618 patients were randomized to receive 7 mg (n=205) or 14 mg (n=216) of teriflunomide or placebo (n=197). The risk of a second clinical attack over 2 years was 35.9% in the placebo group and 24.0% in the teriflunomide 14 mg treatment group (hazard ratio: 0.57, 95% confidence interval: 0.38 to 0.87, p=0.0087). The results from the TOPIC study confirmed the efficacy of teriflunomide in RRMS (including early RRMS with first clinical demyelinating event and MRI lesions disseminated in time and space).

Teriflunomide effectiveness was compared to that of a subcutaneous interferon beta-1a (at the recommended dose of 44 µg three times a week) in 324 randomised patients in a study (TENERE) with minimum treatment duration of 48 weeks (maximum 114 weeks). The risk of failure (confirmed relapse or permanent treatment discontinuation whichever came first) was the primary endpoint. The number of patients with permanent treatment discontinuation in the teriflunomide 14 mg group was 22 out of 111 (19.8%), the reasons being

adverse events (10.8%), lack of efficacy (3.6%), other reason (4.5%) and lost to follow-up (0.9%). The number of patients with permanent treatment discontinuation in the subcutaneous interferon beta-1a group was 30 out of 104 (28.8%), the reasons being adverse events (21.2%), lack of efficacy (1.9%), other reason (4.8%) and poor compliance to protocol (1%). Teriflunomide 14 mg/day was not superior to interferon beta-1a on the primary endpoint: the estimated percentage of patients with treatment failure at 96 weeks using the Kaplan-Meier method was 41.1% versus 44.4% (teriflunomide 14 mg versus interferon beta-1a group, $p=0.595$).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with AUBAGIO in children from birth to less than 10 years in treatment of multiple sclerosis (see Posology and method of administration for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with AUBAGIO in one or more subsets of the paediatric population in multiple sclerosis (see Posology and method of administration for information on paediatric use).

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 (approximately 100%).

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

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

Biotransformation

Teriflunomide is moderately metabolised and is the major circulating moiety detected in plasma. The primary biotransformation pathway to minor metabolites 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. Over 21 days, 60.1% of the administered dose is excreted via feces (37.5%) and urine (22.6%). After the accelerated elimination procedure with cholestyramine, an additional

23.1% was recovered (mostly in feces). After a single IV administration, the total body clearance of teriflunomide is 30.5 ml/h.

Accelerated Elimination Procedure: Cholestyramine and activated charcoal

Elimination can be accelerated by either of the following procedures:

- Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 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.

Linearity/non-linearity

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

Characteristics in specific groups of patients

Gender, Elderly, Paediatric patients

Several sources of intrinsic variability were identified in healthy subjects and MS patients based on the PopPK analysis: age, body weight, gender, race, and albumin and bilirubin levels. Nevertheless, their impact remains limited ($\leq 31\%$).

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the pharmacokinetic of teriflunomide. Therefore no dose adjustment is anticipated in mild and moderate hepatic-impaired patients. The pharmacokinetics of teriflunomide in severe hepatic impairment have not been evaluated

Renal impairment

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

Preclinical safety data

Repeated oral administration of teriflunomide to mice, rats and dogs for up to 3, 6, and 12 months, respectively, revealed that the major targets of toxicity were the bone marrow, lymphoid organs, oral cavity/gastro intestinal tract, reproductive organs, and pancreas. Evidence of an oxidative effect on red blood cells was also observed. Anemia, decreased platelet counts and effects on the immune system, including leukopenia, lymphopenia and secondary infections, were related to the effects on the bone marrow and/or lymphoid organs. The majority of effects reflect the basic mode of action of the compound (inhibition of dividing cells). Animals are more sensitive to the pharmacology, and therefore toxicity, of teriflunomide than humans. As a result, toxicity in animals was found at exposures equivalent or below human therapeutic levels.

Teriflunomide was not mutagenic *in vitro* or clastogenic *in vivo*. Clastogenicity observed *in vitro* was considered to be an indirect effect related to nucleotide pool imbalance resulting from the pharmacology of DHO-DH inhibition. The minor metabolite TFMA (4-trifluoromethylaniline) caused mutagenicity and clastogenicity *in vitro* but not *in vivo*.

No evidence of carcinogenicity was observed in rats and mice.

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

PHARMACEUTICAL PARTICULARS

List of excipients

Tablet core

lactose monohydrate

maize starch

microcrystalline cellulose

sodium starch glycolate (Type A)

hydroxypropylcellulose

magnesium stearate

Tablet coating
hypromellose
titanium dioxide (E171)
talc
macrogol 8000
indigo carmine aluminum lake (E132)

Incompatibilities

Not applicable.

Shelf life

3 years

Special precautions for storage

This medicinal product does not require any special storage conditions.

Nature and contents of container

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

Each wallet is placed in a protective sleeve.

Aluminium-aluminium perforated unit-dose blister packs in cartons containing 10x1 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorization Holder

sanofi-aventis (Thailand) Ltd., Bangkok, Thailand

Marketing Authorization Number

1C 43/60 (NC)

Date of Authorization

27 June 2017

Date of Revision of the Text

CCDS v5 (6 Jun 2019)