For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

This package insert is updated periodically. Please read carefully before using a new pack

Teriflunomide Tablets 14 mg
AUBAGIO®

DESCRIPTION
ACTIVE INGREDIENTS
AUBAGIO® (teriflunomide), is an oral de novo pyrimidine synthesis inhibitor of the DHO-DH enzyme, with the chemical name (Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl)-amide. Its molecular weight is 270.21, and the empirical formula is C12H9F3N2O2 with the following chemical structure: Teriflunomide is a white to almost white powder that is sparingly soluble in acetone, slightly soluble in polyethylene glycol and ethanol, very slightly soluble in isopropanol and practically insoluble in water.

THERAPEUTIC OR PHARMACOLOGICAL CLASS
PHARMACEUTICAL FORM(S)
AUBAGIO® is available as pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side dose strength given as number 14 and engraved with corporate logo on the other side.

COMPOSITION
Active ingredient: Teriflunomide 14 mg
Excipients: lactose monohydrate, corn starch, hydroxypropylcellulose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating for the 14 mg tablet is composed of hypromellose, titanium dioxide, talc, polyethylene glycol and indigo carmine aluminum lake.

NATURE AND CONTENTS OF CONTAINER
Carton of 28 tablets of 14 mg containing 1 wallet composed of 2 folded blister cards of 14 tablets per blister card

INDICATIONS
AUBAGIO® is indicated for the treatment of patients with relapsing forms of multiple sclerosis

DOSAGE AND ADMINISTRATION
GENERAL

The recommended dose of AUBAGIO® is 14 mg orally once daily.

SPECIAL POPULATIONS
Children
The safety and effectiveness of AUBAGIO® in pediatric patients with MS below the age of 18 years have not yet been established.

Elderly
Clinical studies of AUBAGIO® did not include patients over 65 years old. AUBAGIO® should be used with caution in patients aged over 65 years.

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 Section Contraindication and Section Special Populations).

Renal impairment
No dosage adjustment is necessary for patients with severe renal impairment (see Section Special Population).

ADMINISTRATION
AUBAGIO® can be taken with or without food.

CONTRAINDICATIONS
AUBAGIO® is contraindicated in patients with:
- known hypersensitivity to teriflunomide, leflunomide or to any of the inactive ingredients in the formulation
- severe hepatic impairment
- 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 Section Pregnancy)

WARNINGS

HEPATIC EFFECTS
Elevations of liver enzymes have been observed in patients receiving AUBAGIO®.
In placebo-controlled trials, ALT greater than three times the upper limit of normal (ULN) occurred in 61/1045 (5.8%) and 62/1002 (6.2%) of patients on teriflunomide 7 mg and 14 mg, respectively, and 38/997 (3.8%) of patients on placebo, during the treatment period. These elevations occurred mostly within the first 6 months of treatment. Half of the cases returned to normal without drug discontinuation. In clinical trials, teriflunomide was discontinued if the ALT elevation exceeded 3 times the ULN twice. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of AUBAGIO®. One additional clinically significant case of "toxic hepatitis" was reported in a 35-year-old female patient. Although the etiology of the hepatic event remained unclear, a causal role of teriflunomide in this case is possible.

Obtain serum transaminase and bilirubin levels within 6 months before initiation of AUBAGIO® therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO®. Consider monitoring when AUBAGIO®is given with other potentially hepatotoxic drugs. Consider discontinuing AUBAGIO® if serumtransaminase increase (greater than three times the ULN) is confirmed. Monitor serum transaminase and bilirubin on AUBAGIO® therapy,

particularly in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. If liver injury is suspected to be AUBAGIO®-induced, discontinue teriflunomide and start an accelerated elimination procedure (see Section Elimination Procedure) and monitor liver tests weekly until normalized. If teriflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of teriflunomide therapy may be considered.

USAGE IN WOMEN OF CHILD-BEARING POTENTIAL / PREGNANCY

Animal data suggest risks to the fetus. Women of childbearing potential must use effective contraception to avoid pregnancy while taking AUBAGIO®. If AUBAGIO® is stopped, women should continue contraception until teriflunomide plasma concentrations have been checked to be equal to 0.02 μg/mL or lower. Women, who are planning a pregnancy or are pregnant, should be advised that an accelerated elimination procedure can be used to quickly decrease the plasma concentration of teriflunomide. Without the accelerated elimination procedure, on average it takes 8 months to reach plasma concentrations less than or equal to 0.02 μg/mL; however due to individual variation in drug clearance it may take up to 2 years. The accelerated elimination could be used at any time after discontinuation of AUBAGIO® (see Section Elimination).

PRECAUTIONS

BLOOD PRESSURE EFFECTS

In placebo-controlled studies, mean change from baseline to endpoint value in systolic blood pressure was 2.3 mmHg and 2.7 mmHg for AUBAGIO® 7 mg and 14 mg, respectively, and 0.6 mmHg for placebo. The change from baseline in diastolic blood pressure was 1.4 mmHg and 1.9 mmHg for AUBAGIO®7 mg and 14 mg, respectively, and -0.3 mmHg for placebo. Hypertension was reported as an adverse reaction in 3.1% and 4.3% of patients treated with 7 mg or 14 mg of AUBAGIO®, compared with 1.8% on placebo. Check blood pressure before start of AUBAGIO® and periodically thereafter. Blood pressure elevation should be appropriately managed during treatment with AUBAGIO®.

INFECTIONS

In placebo-controlled studies of AUBAGIO®, no overall increase in the risk of serious infections was observed with teriflunomide 7 mg (2.2%) or 14 mg (2.7%) compared to placebo (2.2%). However, one fatal case of klebsiella pneumonia sepsis occurred in a patient taking teriflunomide 14 mg for 1.7 years. In clinical studies with AUBAGIO®, cytomegalovirus hepatitis reactivation and tuberculosis have been observed.

However, based on the immunomodulatory effect of AUBAGIO®, if a patient develops a serious infection, consider suspending treatment with AUBAGIO®, and reassess the benefits and risks prior to re-initiation of therapy. Due to the prolonged half-life of elimination of teriflunomide, accelerated elimination with cholestyramine or charcoal may be considered (see Section Elimination). Instruct patients receiving AUBAGIO® 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 EFFECTS
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. 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.

HEMATOLOGIC 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 < 1.5x109/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 <0.8x109/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® assessed during AUBAGIO® therapy. Further monitoring should be based on signs and symptoms suggestive of infection.

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.

SKIN REACTIONS
No cases of severe skins reactions have been reported with teriflunomide in the clinical trials. Cases have been reported rarely in the postmarketing setting (including Stevens-Johnson syndrome, and toxic epidermal necrolysis).

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 elimination procedure initiated immediately. In such cases patients should not be re-exposed to teriflunomide (see section Contraindication).

PERIPHERAL NEUROPATHY
Cases of peripheral neuropathy have been reported in patients receiving AUBAGIO®. Most patients improved after discontinuation of AUBAGIO®. However, there was a wide variability in final outcome, i.e. in some patients the neuropathy resolved and some patients had persistent symptoms. If a patient taking AUBAGIO® develops a confirmed peripheral neuropathy, consider discontinuing AUBAGIO® therapy and performing the accelerated elimination procedure.

CONCOMITANT USE OF IMMUNOSUPPRESSIVE OR IMMUNOMODULATING THERAPIES
As leflunomide is the parent compound of teriflunomide, co-administration of teriflunomide with leflunomide is not recommended.
Co-administration with antineoplastic or immunosuppressive therapies used for treatment of multiple sclerosis has not been evaluated. Safety studies, in which teriflunomide was concomitantly administered with other immune modulating therapies for up to one year (interferon beta, glatiramer acetate) did not reveal any specific safety concerns. The long term safety of these combinations in the treatment of multiple sclerosis has not been established.

ELIMINATION PROCEDURE
Teriflunomide is eliminated slowly from the plasma. When desired, an accelerated elimination procedure can be used (see Section Elimination).

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

POTENTIAL FOR OTHER DRUGS TO AFFECT AUBAGIO®
Based on *in vitro* studies, teriflunomide is a substrate of the efflux transporter BCRP. BCRP inhibitors (such as cyclosporine, eltrombopag, gefitinib) may increase exposure of teriflunomide.

Potent CYP and transporter inducers:
Rifampin did not affect the pharmacokinetics of teriflunomide**.**

POTENTIAL FOR AUBAGIO® TO AFFECT OTHER DRUGS

Effect of teriflunomide on CYP2C8 substrates:
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. The magnitude of interaction could be higher at the recommended repaglinide dose. Therefore, monitoring patients with concomitant use of drugs metabolized by CYP2C8,

such as repaglinide, paclitaxel, pioglitazone, or rosiglitazone is recommended as they may have higher exposure.

Effect of teriflunomide on warfarin
A 25% decrease in peak international normalized ratio (INR) was observed when teriflunomide was coadministered with warfarin as compared with warfarin alone. Therefore, when warfarin is coadministered with teriflunomide, close INR follow-up and monitoring is recommended.

Effect of teriflunomide on oral contraceptives
There was an increase in mean ethinylestradiol Cmax and AUC0-24 (1.58- and 1.54-fold, respectively) and levonorgestrel Cmax and AUC0-24 (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 substrates:
Repeated doses of teriflunomide decreased mean Cmax and AUC of caffeine (CYP1A2 substrate) by 18% and 55 %, respectively, suggesting that in vivo teriflunomide is a weak inducer of CYP1A2. Therefore, drugs metabolized 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 efficacy of these drugs.

Effect of teriflunomide on organic anion transporter 3 (OAT3) substrates:
There was an increase in mean cefaclor Cmax 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, penicillin G, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution should be observed.

Effect of teriflunomide on BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates:
There was an increase in mean rosuvastatin Cmax 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. If used together, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (eg, methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (eg, simvastatin, atorvastatin pravastatin, methotrexate, nateglinide, repaglinide, rifampin) concomitant administration of teriflunomide should also be undertaken with caution. Monitor patients closely for signs and symptoms of excessive exposure to the drugs and consider reduction of the dose of these drugs.

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

PREGNANCY
There are no adequate and well-controlled studies of AUBAGIO® in pregnant women. However, based on animal studies, AUBAGIO® may increase the risk of fetal death or teratogenic effects when administered to pregnant women. Teriflunomide is contraindicated in pregnancy (see Section Contraindication).

Human teriflunomide plasma concentration less than 0.02 μg/mL is expected to have minimal risk based on available animal data. If AUBAGIO® is to be discontinued, an accelerated elimination procedure is recommended (see Section Usage in women of child bearing potential/ pregnancy and Section Elimination).

Use in males
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 observed at steady state after 14 mg of oral teriflunomide. There were no external malformations in the offspring of male rats administered teriflunomide for at least 10 weeks prior to mating with untreated female rats. Genotoxicity was not observed in vivo in 3 species. The NOEL in the in vitro chromosome aberration test in human lymphocytes was 6 times greater than the mean human exposure at the 14 mg dose of teriflunomide.

Labor and Delivery
There is no adequate information regarding the effects of AUBAGIO® on labor and delivery in pregnant women.

LACTATION

Animal studies have shown excretion of teriflunomide in breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from AUBAGIO® a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
AUBAGIO® has no or negligible influence on the ability to drive and use machines.

ADVERSE REACTIONS
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).

In clinical trials, the most frequent adverse reactions for AUBAGIO® (incidence ≥10% and ≥2% greater than placebo) in the placebo-controlled studies were headache, diarrhea, nausea, alopecia, ALT increased.

CLINICAL TRIAL EXPERIENCE

A total of 2047 patients on teriflunomide (7 or 14 mg once daily) and 997on placebo constituted the safety population in the pooled analysis of placebo controlled studies in patients with relapsing forms of MS (RMS).

Table 1 Adverse Reactions in placebo controlled studies (occurring in >=1% of patients, and reported for teriflunomide 7 mg or 14 mg at >= 1% higher rate than for placebo)

		teriflunomide	
PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=997)	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			

		teriflunomide	
PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=997)	7 mg (N=1045)	14 mg (N=1002)
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%)

		teriflunomide	
PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=997)	7 mg (N=1045)	14 mg (N=1002)
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%)

Polyneuropathy

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), was reported more frequently in patients taking AUBAGIO® than in patients taking placebo. In the pivotal, placebo-controlled studies, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.4% (13 patients) and 1.9% (17 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 teriflunomide14 mg).
Five of them recovered following treatment discontinuation. Not all cases of peripheral neuropathy resolved with continued treatment.

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
• 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
SIGNS AND SYMPTOMS
There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily up to 14 days was well tolerated by healthy subjects.

MANAGEMENT
In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination (See Section Elimination).

PHARMACODYNAMICS

MODE OF ACTION/PHARMACODYNAMIC CHARACTERISTICS
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 Properties

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.

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.

In a clinical study, teriflunomide-treated patients mounted appropriate immune responses to a seasonal influenza vaccination, consistent with the preservation of a response to booster vaccine. Patients in both 7 mg and 14 mg teriflunomide treated groups reached post-vaccination antibody titres consistent with seroprotection: over 90% of patients achieved post-vaccination antibody titers ≥40 for H1N1 and B strains in both 7 mg and 14 mg treatment groups. For H3N2 strain, titers ≥40 were achieved in >90% of patients in the 7 mg group, and in 77% of patients in the 14 mg group In a second pharmacodynamic study, the immune response to inactivated rabies vaccine, neo antigen, was investigated in a randomized, double blind, placebo-controlled study in healthy subjects. The geometric mean titers to rabies vaccine were lower in the teriflunomide group than placebo group, achieving postvaccination treatment ratio of teriflunomide versus placebo [90% CI] of 0.53 [0.35, 0.81] at the end of the vaccination regimen. However, following vaccination, anti-rabies antibody levels were above the 0.5 IU/mL, the threshold for seroprotection, in all subjects. In the same study, the capacity to mount a skin delayed-type hypersensitivity reaction to recall antigens such as Candida albicans, Trichophyton or Tuberculin Purified Derived Protein in subjects receiving teriflunomide did not differ from placebo.

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 10 to 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/CLINICAL STUDIES

The efficacy of AUBAGIO® was established in two phase 3, placebo-controlled studies in patients with relapsing forms of RMS and one phase 3, placebo-controlled study in patients with early MS (i.e., with a first clinical episode).

Study 1 (EFC6049/TEMSO) was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg in patients with relapsing forms of multiple sclerosis (RMS) over 108 weeks. All patients had a definite diagnosis of MS exhibiting 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. Subjects had not received interferon-beta for at least 4 months or any other preventive MS medications for at least 6 months before entering the study, nor were these medications permitted during the study. Neurological evaluations were performed at screening, every 12 weeks until week 108 and at unscheduled visits for suspected relapse. MRI was performed at screening, weeks, 24, 48, 72, and 108. The primary endpoint was the annualized relapse rate (ARR).

A total of 1088 patients with RMS were randomized to receive 7 mg (n=366) or 14 mg (n=359) of teriflunomide or placebo (n=363). 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 mean disease duration was 5.33 years, and the mean EDSS at baseline was 2.68. A total of 91.4% had relapsing remitting MS (RRMS) and 8.6% had a progressive form of MS with relapses. The mean time on placebo was 631 days, on 7 mg AUBAGIO® 635 days, and on 14 mg AUBAGIO® 627 days.

The ARR was significantly reduced in patients treated with either 7 mg or 14 mg of "Aubagio" compared to patients who received placebo (Table 2). There was a consistent reduction of the ARR noted in subgroups defined by sex, age group, prior MS therapy, and baseline disease activity.
The risk of disability progression sustained for 12 weeks (as measured by at least a 1-point increase from baseline EDSS ≤ 5.5 or a 0.5 point increase for those with a baseline EDSS > 5.5) was statistically significantly reduced only in the teriflunomide 14 mg group compared to placebo (Table 2 and Figure 1).

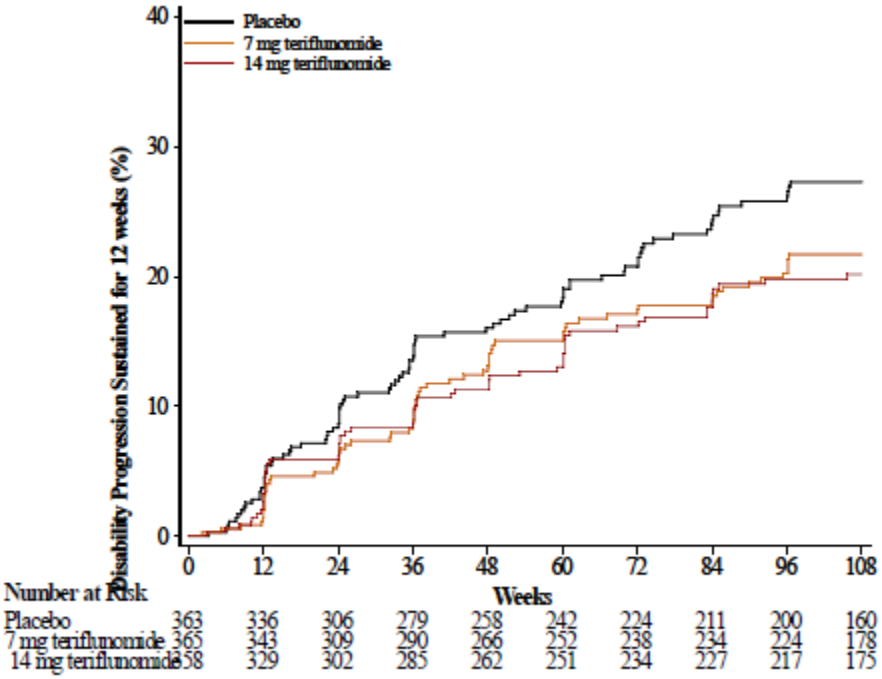
The effect of teriflunomide on several magnetic resonance imaging (MRI) variables including the total lesion volume of T2 and hypointense T1 lesions was assessed. The change in total lesion volume from baseline was significantly lower in the 7 mg and 14 mg groups than in the placebo group. Patients in both teriflunomide groups had significantly fewer gadolinium-enhancing lesions per T1-weighted scan than those in the placebo group (Table 2).

Table 2 - Clinical and MRI Results of EFC6049/TEMSO Study

	TN 14 mg N=358	TN 7 mg N=365	Placebo N=363
Clinical Endpoints			
Annualized relapse rate (primary endpoint)	0.369	0.370	0.539
	(p = 0.0005)	(p = 0.0002)	
Relative risk reduction	31%	31%	
Percent of patients remaining relapse-free at week 108	56.5%	53.7%	45.6%
	(p = 0.0030)	(p = 0.0104)	
Percent disability progression at week 108	20.2%	21.7%	27.3%
	(p = 0.028)	(p = 0.084)	
Hazard ratio	0.70	0.76	
Relative risk reduction	30%	24%	
MRI Endpoints			
Median change from baseline in total lesion volume1 (mL) at week 108	0.345	0.755	1.127
Percent change relative to placebo	(p = 0.0003)2	(p= 0.0317)2	
	69%	33%	
Mean number of Gd-enhancing T1-lesions per scan	0.261	0.570	1.331
Relative reduction	(p < 0.0001)	(p < 0.0001)	
	80%	57%	

[1] Total lesion volume: sum of T2 and hypointense T1 lesion volume in mL
[2] p-values based on cubic root transformed data for total lesion volume

Figure 1 Kaplan- Meier plot of time to disability progression sustained for 12 weeks - intent-to-treat population



Study 2 (EFC10531/TOWER) was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg in patients with relapsing forms of multiple sclerosis (RMS) with a mean treatment duration of approximately 18 months. All patients had a definite diagnosis of MS exhibiting 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. Subjects had not received interferon-beta or any other preventive MS medications for at least 3 months before entering the study nor were these medications permitted during the study. Neurological evaluations were performed at screening, at every 12 weeks until completion, and at unscheduled visits for suspected relapse. The primary endpoint was the annualized relapse rate (ARR).

A total of 1169 patients were randomized to receive 7 mg (n=408) or 14 mg (n=372) of teriflunomide or placebo (n=389). The mean age was 37.9 years the mean disease duration was 5.16 years, and the mean EDSS at baseline was 2.7 (median EDSS score at baseline was 2.50). A majority of the patients had relapsing remitting MS (97.5%). The mean time on placebo was 571 days, on 7 mg AUBAGIO® 552 days, and on 14 mg AUBAGIO® 567 days.

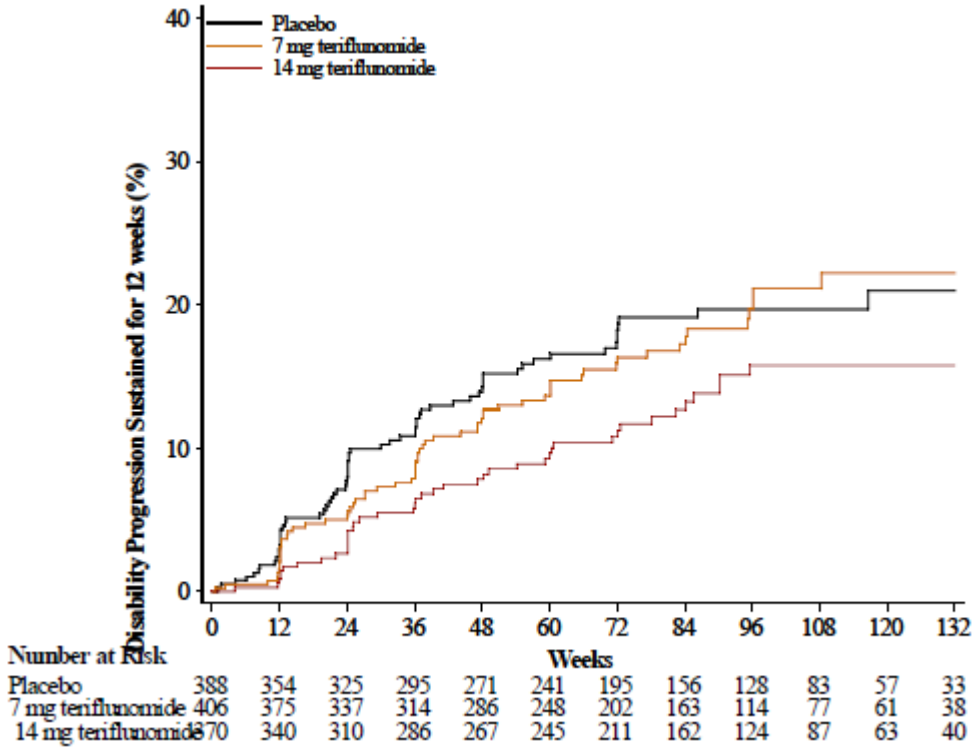
The ARR was significantly reduced in patients treated with either 7 mg or 14 mg of AUBAGIO® compared to patients who received placebo (see Table 3). There was a consistent reduction of the ARR noted in subgroups defined by sex, age group, prior MS therapy, and baseline disease activity.

The risk of disability progression sustained for 12 weeks (as measured by at least a 1-point increase from baseline EDSS ≤ 5.5 or a 0.5 point increase for those with a baseline EDSS > 5.5) was statistically significantly reduced only in the teriflunomide 14 mg group compared to placebo (Table 3and Figure 2).

Table 3 - Clinical Results of EFC10531/TOWER Study

	TN 14 mg N=370	**TN 7 mg N=407**	**Placebo N=388**
Clinical Endpoints			
Annualized relapse rate (primary endpoint)	0.319	0.389	0.501
	(p = 0.0001)	(p = 0.0189)	
Relative risk reduction	36.3%	22.3%	
Percent of patients remaining relapse-free at week 108	57.1%	58.2%	46.8%
	(p < 0.0001)	(p = 0.0016)	
Percent disability progression at week 108	15.8%	21.1%	19.7%
	(p = 0.044)	(p = 0.762)	
Hazard ratio	0.69	0.96	
Relative risk reduction	31%	4%	

Figure 2 Kaplan- Meier plot of time to disability progression sustained for 12 weeks – ITT population



Study 3 (EFC6260/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 early MS (i.e., a first clinical episode). Patients had a first neurological event occurring within 90 days of randomization, with 2 or more T2 lesions at least 3 mm in diameter that were characteristic of MS. 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 mean age of the study population was 32.1 years and the mean time since first neurological event was 1.85 months, 59.1% of the patients entered the study with monofocal episode, and 40.9% with a multifocal episode. The mean time on placebo was 464 days, on 7 mg AUBAGIO® 464 days, and on 14 mg AUBAGIO® 493 days.

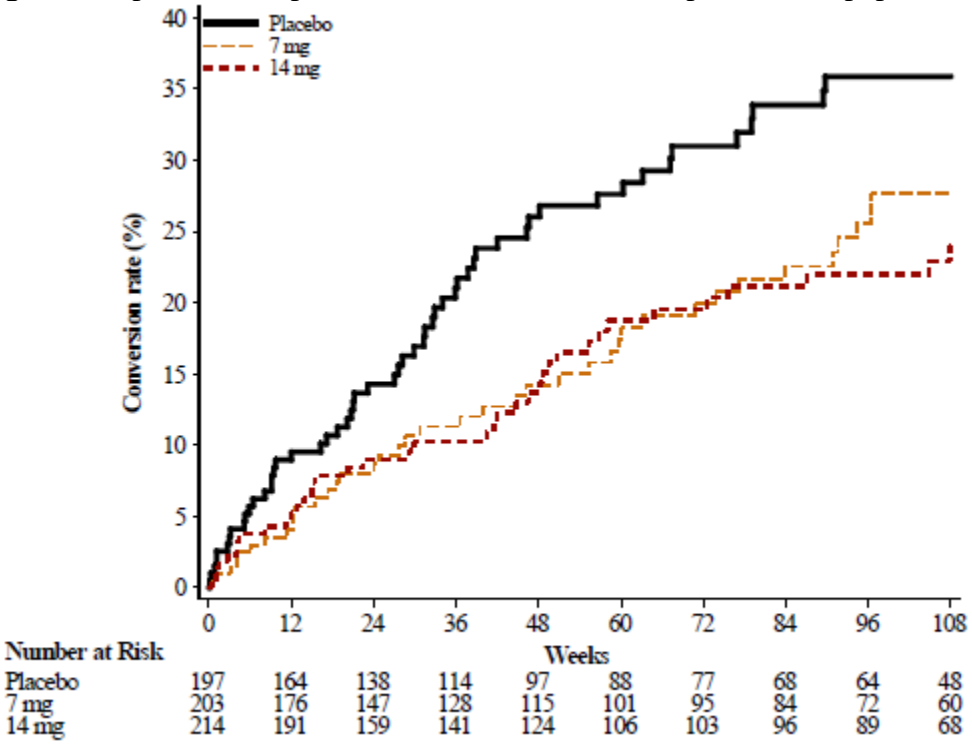
The risk of a second clinical episode was statistically significantly reduced in the teriflunomide 7 mg and 14 mg group compared to placebo (Table 4 and Figure 3).The risk of a second clinical episode or a new MRI lesion (a new Gd-enhancing T1 lesion or a new T2 lesion) was statistically significantly reduced in the teriflunomide 7 mg and 14 mg group compared to placebo (Table 4and Figure 3).

Table 4 - Clinical and MRI Results of EFC6260/TOPIC

	TN 14 mg N=214	TN 7 mg N=203	Placebo N=197
Clinical endpoints			
Percent of patients remaining free of a second clinical episode at week 108 (primary endpoint)	76.0% (p=0.0087)	72.4% (p=0.0271)	64.1%
Hazard ratio	0.574	0.628	
Percent of patients remaining free of a second clinical episode and new MRI lesion at week 108	28.5% (p=0.0003)	26.7% (p=0.0020)	13.0.0%
Hazard ratio	0.651	0.686	
MRI endpoints			
Median change from baseline in Total lesion volume1 (mL) at week 108	-0.227 (p = 0.0374)2	0.047 (p= 0.7789)2	-0.202
Mean number of Gd-enhancing T1-lesions per scan	0.395 (p = 0.0008)	0.749 (p = 0.4366)	0.953

[1] Total lesion volume: sum of T2 and hypointense T1 lesion volume in mL
[2] p-values based on cubic root transformed data for total lesion volume

Figure 3 Kaplan- Meier plot of time to second clinical episode- ITT population (EFC6260/TOPIC)



The effect of teriflunomide on MRI activity was also demonstrated in a fourth study, 2001, a randomized, double-blind, placebo-controlled study of MS subjects with relapse. A total of 179 patients were treated with twice the usual dose for the first week and then received 7 mg (n=61) or 14 mg (n=57) of teriflunomide or placebo (n= 61) for the remainder of the 36-week treatment period. The primary endpoint was the average number of unique active lesions/MRI scan during treatment. MRI was performed at baseline, 6 weeks, 12 weeks, 18 weeks, 24 weeks, 30 weeks and 36 weeks. Baseline demographics were consistent across treatment groups. The mean number of unique active lesions per brain MRI scan during the 36-week treatment period was lower in patients treated with teriflunomide 14 mg (0.98) and 7 mg (1.06) as compared to placebo (2.69), the difference being statistically significant for both (p=0.0052 and p=0.0234, respectively).

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 randomized 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. Teriflunomide 7 mg and 14 mg/day were not statistically superior to interferon beta-1a on the primary end point. The estimated percentage of patients with treatment failure at 96 weeks using the Kaplan-Meier method was 58.8% versus 44.4% (teriflunomide 7 mg versus interferon beta-1a group, p=0.5190) and 41.1% versus 44.4% (teriflunomide 14 mg versus interferon beta-1a group, p=0.5953).

PHARMACOKINETICS

Based on a population pharmacokinetic analysis of teriflunomide using data from healthy subjects and MS patients, median $t_{1/2z}$ was approximately 18 and 19 days after repeated doses of 7 mg and 14 mg, respectively. It takes approximately 3 months, respectively, to reach steady-state concentrations. The estimated AUC accumulation ratio is approximately 30 after repeated doses of 7 mg or 14 mg.

ABSORPTION

Median time to reach maximum plasma concentrations occurs between 1 to 4 hours post-dose following oral administration of teriflunomide, with high bioavailability (~100%).

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

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

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.

METABOLISM

Teriflunomide is moderately metabolized and is the major circulating moiety detected in plasma. The primary biotransformation pathway to minor metabolites of teriflunomide is hydrolysis, with oxidation being a minor pathway. Secondary pathways involve oxidation, N-acetylation and sulfate conjugation.

ELIMINATION

Teriflunomide is excreted in the gastrointestinal tract mainly through the bile as unchanged drug and possibly 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.

<u>Accelerated Elimination Procedure: Cholestyramine and activated charcoal</u>

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 6 months to reach plasma concentrations less than 0.25 mg/L, Due to individual variations in drug clearance, it may take as long as 2 years. An accelerated elimination procedure could be used at any time after discontinuation of AUBAGIO®. Elimination can be accelerated by either of the following procedures:

- Administration of 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.

SPECIAL POPULATIONS

Gender, Elderly, Paediatric patients

Several sources of intrinsic variability were identified in healthy subjects and MS patients based on the population pharmacokinetic 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. The pharmacokinetics of teriflunomide in severe hepatic impairment have not been evaluated (see Section Contraindication).

Renal impairment

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

CARCINOGENICITY

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of teriflunomide up to the maximally tolerated dose of 4 mg/kg/day (approximately 1/2 the maximum human teriflunomide systemic exposure based on AUC0-24). Moreover, no evidence of carcinogenicity was observed in a 2-year bioassay in mice at oral doses of teriflunomide up to the maximally tolerated dose of 12 mg/kg/day (approximately 5-6 times the maximum human teriflunomide systemic exposure based on AUC0-24).

MUTAGENICITY

Teriflunomide was not mutagenic, as demonstrated by negative Ames and hypoxanthine-guaninephosphoribosyl transferase (HPRT) tests.

4-Trifluoromethylaniline (4-TFMA), a minor metabolite of teriflunomide, was mutagenic in the Ames and HPRT tests.

GENOTOXICITY

Teriflunomide was not clastogenic in vivo in the 3 species tested: mouse (micronucleus test), Chinese hamster (chromosome aberration test), and rat (repeat-dose chromosome aberration test). Positive results were seen in an in vitro chromosome aberration test in human lymphocytes after 3-hour treatment both with and without metabolic activation. Supplementation with uridine reduced the cytotoxicity and the magnitude of the clastogenic effect. The positive response is considered to be an indirect effect due to the pharmacologic mechanism of action of nucleotide pool imbalance resulting from DHODH inhibition. The highest tested concentration without effect in the in vitro chromosome aberration test in human lymphocytes was approximately 6

times greater than the maximum human teriflunomide exposure at the 14 mg dose. Furthermore, teriflunomide was negative in all other genotoxicity studies.

4-Trifluoromethylaniline (4-TFMA), a minor metabolite of teriflunomide, was clastogenic in the in vitro chromosome aberration test in Chinese hamster cells. 4-TFMA was not clastogenic in vivo in the 2 species tested: mouse (micronucleus test) and Chinese hamsters (chromosome aberration test). Equivocal results were seen in the unscheduled DNA synthesis (UDS) test in rat liver. The 4-TFMA concentrations used in the in vitro genotoxicity studies are at least 1000 times higher than the mean plasma levels in patients exposed to 4-TFMA as a metabolite of teriflunomide at the 14 mg dose.

TERATOGENICITY

In oral studies conducted in pregnant rats and rabbits, AUBAGIO® demonstrated developmental toxicity, including teratogenicity and embryolethality. In rats, exposure at the no-observed-effect-level (1.0 mg/kg/day) for teratogenicity and embryolethality was less than the human exposure at 14 mg/day. Primary malformations in rats were microophthalmia or anophthalmia; accompanied by aplasia lentis and decreased orbit size; hydrocephalus; edematous fetus; hematocyst on parietal bone; brachygnathia inferior; bent tarsal region of the hindpaw; fragmented, dysplastic and fused skull bones; multiple anomalies of the vertebral column; and alterations of ribs and pectoral girdle. In rabbits, exposure at the no-observed-effect level (1.0 mg/kg/day) was also less than the human exposure at 14 mg/day. Malformations of the forelimbs (short and misshapen ulna, absent radius, brachydactyly); absence of kidney, adrenal, and ureter; cleft lip and palate; growth retardation; hyperflexion of the forepaws; malpositioned branch of the carotid; anomalies of the lung lobes and sternebrae; and delayed ossification of several bones were observed.

In a study where AUBAGIO® was administered to pregnant rats during gestation and lactation, AUBAGIO® did not affect sexual maturation, learning, memory, motor activity, startle response, reproductive ability, estrous cycles, mating behavior, fertility and fecundity, or early embryonic development. Adverse effects observed in the offspring at 0.3 mg/kg/day included limb defects and impaired coat growth sometimes associated with skin discoloration. Corneal opacity, eye discharge, and negative pupillary reflex occurred in a few pups. Mean fetal weight per litter was slightly decreased. Effects on coat growth resolved but limb defects persisted in a few pups after weaning. The no-observed-effect-level in the offspring was 0.10 mg/kg/day. Of importance, similar adverse findings were not seen in an exploratory study where AUBAGIO® was administered at 1.0 mg/kg/day during the gestation period and not during lactation to avoid transfer of AUBAGIO® in the milk. Under those conditions, the no-observed-effect-level in the offspring was 1.0 mg/kg/day.

IMPAIRMENT OF FERTILITY

In separate male and female fertility studies, oral administration of AUBAGIO® to rats prior to and during mating (both sexes), and continuing to Day 6 of gestation (females) had no effect on fertility up to the highest doses tested (10 and 8.6 mg/kg/day in males and females, respectively), which is approximately 7 and 6 times the RHD on a mg/m2 basis, respectively. However, effects on the fetus were observed in the female fertility study that consisted of embryolethality and isolated malformations at doses of 2.6 mg/kg/day and above and decreased fetal body weight

down to the lowest dose tested of 0.84 mg/kg/d. In males, a slight decrease in epididymal sperm count (-12.5%) was observed at the highest dose (10 mg/kg/day) with no microscopic correlate in the testes or epididymides.

Storage: Store below 30ºC. Keep out of the sight and reach of children

Shelf life: 36 months

Manufactured by:
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Compiegne, France

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Source: Teriflunomide CCDS version 4 dated 25th August 2016

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