PRODUCT MONOGRAPH

Pr AUBAGIO®

Teriflunomide tablets
14 mg

Immunomodulator Agent

Sanofi Genzyme, a division of sanofi-aventis Canada Inc.
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PrAUBAGIO®

Teriflunomide tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Film-coated tablet/14 mg	corn starch, hydroxypropylcellulose, hypromellose, indigo carmine aluminum lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, talc, titanium dioxide, polyethylene glycol

INDICATIONS AND CLINICAL USE

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

AUBAGIO should only be prescribed by clinicians who are experienced in the diagnosis and management of multiple sclerosis.

Pediatrics (< 18 years of age):

The safety and effectiveness of AUBAGIO have not been established in pediatric patients and AUBAGIO is not recommended in this patient population.

Geriatrics (> 65 years of age):
Clinical studies of AUBAGIO did not include patients over 65 years old. AUBAGIO should be used with caution in patients aged 65 years and over. Physicians who choose to treat geriatric patients should consider that treatment with AUBAGIO in the context of a greater frequency of other concomitant diseases and concomitant drug therapy warrants caution and may necessitate additional or more frequent monitoring (see WARNINGS AND PRECAUTIONS, Special Populations - Geriatrics).

CONTRAINDICATIONS

AUBAGIO (teriflunomide) is contraindicated in patients:

- **with known hypersensitivity to teriflunomide, leflunomide (the parent compound) or to any of the nonmedicinal ingredients in the formulation**
- **who are currently treated with leflunomide**
  Co-administration of teriflunomide with leflunomide is contraindicated.
- **with severe hepatic impairment (see WARNINGS AND PRECAUTIONS, Hepatic/Pancreatic).**
- **who are pregnant or women of childbearing potential not using reliable contraception (see WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction).** AUBAGIO may cause fetal harm when administered to a pregnant woman. Pregnancy must be excluded before start of treatment.
- **with immunodeficiency states (e.g. AIDS)**
- **with impaired bone marrow function or significant anemias, leucopenia, neutropenia or thrombocytopenia**
- **with serious active infections**

WARNINGS AND PRECAUTIONS

HEPATOTOXICITY and RISK OF TERATOGENICITY

Hepatotoxicity
Severe liver injury including fatal liver failure occurred rarely in the post marketing setting. Concomitant use of AUBAGIO with other potentially hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for at least six months after starting AUBAGIO (see WARNINGS AND PRECAUTIONS, Hepatic/Pancreatic). If drug induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or charcoal (see WARNINGS AND PRECAUTIONS, Accelerated Elimination Procedure). AUBAGIO is contraindicated in patients with severe hepatic impairment. ***Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.***

Risk of Teratogenicity
Based on animal data, AUBAGIO may cause major birth defects if used during pregnancy. Pregnancy must be excluded before starting AUBAGIO. AUBAGIO is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during AUBAGIO treatment or prior to the completion of an accelerated elimination procedure after AUBAGIO treatment (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Reproduction, Accelerated Elimination Procedure and Special Populations).

General

Accelerated Elimination Procedure

Teriflunomide is eliminated slowly from the plasma.

Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mg/L, however, 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 a gradual return of disease activity if the patient had been responding to AUBAGIO treatment.

Both cholestyramine and activated powdered charcoal may interact with the absorption of some concomitant medications. In particular, it can 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 charcoal. Use of alternative contraceptive method is recommended.

Lactose

Because AUBAGIO tablets contain lactose, patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption, should not take AUBAGIO.

Cardiovascular

In the multiple sclerosis placebo-controlled studies, mean change from baseline to endpoint value in systolic blood pressure was 2.6 mmHg for AUBAGIO 14 mg, and -0.8 mmHg for placebo. The change from baseline in diastolic blood pressure was 1.8 mmHg for AUBAGIO 14 mg and -0.5 mmHg for placebo.

Hypertension was reported as an adverse reaction in 4.2% of patients treated with 14 mg of AUBAGIO, compared with 2% on placebo for up to 2 years in the placebo controlled trials. During a long-term extension safety study, new onset hypertension was reported as a treatment emergent adverse event in 13.4% of patients overall who were treated with teriflunomide 14 mg

for a median duration of approximately 5 years. At each 6-month interval during long-term treatment, treatment emergent adverse events of new onset hypertension were reported in up to 3% of patients treated with AUBAGIO. Check blood pressure before the initiation of treatment with AUBAGIO and periodically throughout treatment. Elevated blood pressure should be appropriately managed during treatment with AUBAGIO.

Hematologic

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 AUBAGIO as compared to baseline. The decrease in mean WBC count occurred during the first 6 weeks and WBC count remained at the decreased level during treatment (see ADVERSE REACTION).

The majority of patients recovered from decreased neutrophils and/or lymphocyte cell counts in less than 8 weeks, whether continuing on AUBAGIO or after discontinuation.

Rare cases of pancytopenia, agranulocytosis and thrombocytopenia have been reported in the postmarketing setting with leflunomide. A similar risk is expected for teriflunomide.

Obtain a complete blood cell count (CBC) within 6 months before initiating treatment with AUBAGIO and periodically during treatment. Further monitoring should be based on signs and symptoms suggestive of infection.

In any situation in which the decision is made to switch to or from AUBAGIO, from or to another agent with a known potential for hematologic suppression, monitoring for hematologic toxicity is recommended, because there will be overlap of systemic exposure to both compounds, due to the slow elimination from plasma of AUBAGIO and some of the other therapies (eg, natalizumab, fingolimod). Use of an accelerated elimination procedure may decrease this risk when switching to another therapy, but may also potentially result in return of disease activity if the patient had been responding to AUBAGIO treatment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics; WARNINGS AND PRECAUTIONS, Accelerated Elimination Procedure).

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 hematological disorders is increased. If such effects occur, the accelerated elimination procedure should be considered.

Hepatic/Pancreatic

Hepatic

Liver function abnormalities have been reported in some patients treated with teriflunomide in clinical trials. Severe liver injury including fatal liver failure occurred rarely in the post marketing setting. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO. Patients with pre-existing acute or

chronic liver disease, or those with serum alanine aminotransferase (ALT) greater than two times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with AUBAGIO. AUBAGIO is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS).

Elevations of liver enzymes have been observed in patients receiving AUBAGIO.
In placebo-controlled trials, ALT greater than three times the ULN occurred in 44/786 (5.6%) of patients on teriflunomide 14 mg and 30/806 (3.7%) of patients on placebo, during the treatment period of up to 2 years. 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 on two consecutive tests.

Of the patients who underwent discontinuation of AUBAGIO and accelerated elimination in controlled trials, serum transaminase levels returned to normal within approximately 2 months.

In controlled clinical trials, one serious case of "toxic hepatitis" was reported in a 35-year-old female patient. The patient developed ALT 32 times the ULN and jaundice 5 months after initiation of AUBAGIO 14 mg treatment. The patient was hospitalized for 5 weeks and recovered after plasmapheresis and cholestyramine accelerated elimination procedure. Although the etiology of the hepatic event remained unclear, a causal role of teriflunomide in this case is possible.

Cases of drug-induced liver injury (DILI) have been observed in the post-marketing setting, sometimes life-threatening (see ADVERSE REACTIONS, Post Market Adverse Events). The time to onset of DILI ranged from days to years after initiating treatment with AUBAGIO. Drug-induced liver injury events were reported in patients with and without relevant risk factors, such as a history of drug-induced hepatotoxicity or concomitant use of other hepatotoxic drugs, including some drugs used for managing multiple sclerosis. Due to the potential for severe liver injury, exercise caution and closely monitor patients if other known or potentially hepatotoxic drugs are used in combination with AUBAGIO or if there is a history of drug-induced hepatotoxicity (see WARNINGS AND PRECAUTIONS, Risk of Hepatotoxicity and Teratogenicity).

For all patients, obtain serum transaminase and bilirubin levels within 6 months before initiating treatment with AUBAGIO. Monitor ALT levels at least monthly for at least six months after starting AUBAGIO. Additional monitoring is recommended if AUBAGIO is used with other potentially hepatotoxic drugs or if there is a history of drug-induced hepatotoxicity. Consider discontinuing AUBAGIO if serum transaminase increase (greater than three times the ULN) is confirmed. Monitor serum transaminase and bilirubin on AUBAGIO therapy, particularly in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Patients should be advised to immediately report signs or symptoms of hepatotoxicity. If liver injury is suspected to be teriflunomide-induced, discontinue AUBAGIO and start an accelerated elimination procedure (see WARNINGS AND PRECAUTIONS, General, Accelerated 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.

Due to a potential for additive hepatotoxic effects, alcohol consumption should be avoided during treatment with AUBAGIO.

Hypoproteinemia
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 hypoproteinemia, e.g. in nephrotic syndrome. Teriflunomide is not recommended in patients with conditions of severe hypoproteinemia.

Pancreatitis
Very rare cases of acute symptomatic pancreatitis with no alternative etiologies, have been reported during treatment with teriflunomide in MS patients (see ADVERSE REACTIONS, Postmarket Adverse Reactions). For patients with symptoms of acute pancreatitis that are suspected to be teriflunomide-induced, discontinue AUBAGIO and start an accelerated elimination procedure (see WARNINGS AND PRECAUTIONS, General, Accelerated Elimination Procedure).

Immune

Infections
Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved. If a patient develops a serious infection during treatment, consider suspending treatment with AUBAGIO and using an accelerated elimination procedure (see WARNINGS AND PRECAUTIONS, General, Accelerated Elimination Procedure). Reassess the benefits and risks prior to resumption of therapy. Instruct patients receiving AUBAGIO to report symptoms of infections to a physician.

AUBAGIO is contraindicated in patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections (see CONTRAINDICATIONS). Medications like teriflunomide that have immunomodulatory potential may cause patients to be more susceptible to infections, including opportunistic infections.

In placebo-controlled studies of AUBAGIO, no overall increase in the risk of serious infections was observed with teriflunomide 14 mg 2.5% compared to placebo 2.5%. However, one fatal case of *klebsiella* pneumonia sepsis occurred in a patient taking AUBAGIO 14 mg for 1.7 years. In clinical studies with AUBAGIO, cytomegalovirus hepatitis reactivation has been observed. Fatal infections, especially *Pneumocystis jiroveci* pneumonia and aspergillosis, have been reported in the postmarketing setting, in patients receiving leflunomide for treatment of rheumatoid arthritis. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness which, in addition to rheumatoid disease, may predispose patients to infection.

In clinical studies with AUBAGIO, cases of tuberculosis have been observed. Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection. 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 initiating treatment with AUBAGIO.

Hypersensitivity
Cases of hypersensitivity, angioedema and anaphylactic reaction have been reported during the post-marketing period (see ADVERSE REACTIONS, Post Market Adverse Events).

Advise the patient to discontinue AUBAGIO and seek immediate medical care if any signs or symptoms of anaphylaxis or angioedema occurs.

Concomitant use of Immunosuppressive or Immunomodulating Therapies
As leflunomide is the parent compound of teriflunomide, co-administration of AUBAGIO with leflunomide is contraindicated.

Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated and is not recommended due to the potential risk of additive immune system effects.

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

For switches to or from natalizumab or fingolimod see WARNINGS AND PRECAUTIONS, Hematologic.

Due to the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with AUBAGIO after alemtuzumab is not recommended unless the benefits of AUBAGIO treatment clearly outweigh the risks for the individual patient.

Vaccination
Two clinical studies have shown that teriflunomide treated patients mounted appropriate immune responses when vaccinated with inactivated neoantigen (first vaccination), or recall antigen (reexposure). No clinical data are available on the efficacy and safety of live vaccinations in patients taking AUBAGIO. Vaccination with live vaccines is , however, not recommended. The long half-life of AUBAGIO should be considered when contemplating administration of a live vaccine after stopping AUBAGIO.

Neurologic

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 2.2% (15 patients out of 685) on 14 mg of teriflunomide, compared with 0.6% (4 patients out of 708) on placebo. Treatment was discontinued in 2 patients with confirmed peripheral neuropathy on 14 mg of teriflunomide; one of them recovered following treatment discontinuation. The other case of peripheral neuropathy did not resolve with continued treatment. There have also been reports of peripheral neuropathy in patients receiving leflunomide.

Age older than 60 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking AUBAGIO develops symptoms consistent with peripheral neuropathy, such as bilateral numbness or tingling of hands or feet, consider discontinuing AUBAGIO therapy and performing an accelerated elimination procedure.

Respiratory

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

ILD and worsening of interstitial lung disease have been reported during treatment with leflunomide, the parent compound of teriflunomide. ILD is a potentially fatal disorder and may occur acutely at any time during treatment with a variable clinical presentation. The risk is increased in patients with a history of ILD.

New onset or worsening of pulmonary symptoms, such as persistent 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 (see **WARNINGS AND PRECAUTIONS, General, Accelerated Elimination Procedure**).

Sexual Function / Reproduction

Use in Women of Childbearing Potential
AUBAGIO is contraindicated in women who are pregnant or women of child bearing potential not using reliable contraception. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. If pregnancy does occur during treatment, the drug should be immediately discontinued and an accelerated elimination procedure should be initiated (see WARNINGS AND PRECAUTIONS, General, Accelerated Elimination Procedure). Under these conditions, the patient should be referred to an obstetrician/gynecologist, preferably experienced in reproductive toxicity, for further evaluation and counseling.

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 (see TOXICOLOGY, Teratogenicity). In animal studies, teriflunomide has been shown to be selectively teratogenic and embryolethal in multiple species when administered during pregnancy at doses less than those used clinically.

Women of childbearing potential must not be started on AUBAGIO until pregnancy is excluded and it has been confirmed that they are using reliable contraception (see CONTRAINDICATIONS). Before starting treatment with AUBAGIO, patients must be fully counseled on the potential for serious risk to the fetus (see WARNINGS AND PRECAUTIONS, Risk of Hepatotoxicity and Teratogenicity). 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 fetus.

Upon discontinuing AUBAGIO, it is recommended that all women of childbearing potential not using reliable contraception undergo an accelerated elimination procedure. Women receiving AUBAGIO treatment who wish to become pregnant must discontinue AUBAGIO and undergo an accelerated elimination procedure, which includes verification that teriflunomide plasma concentrations decreases to at least 0.02 mg/L. Human plasma concentrations of teriflunomide less than 0.02 mg/L are expected to have minimal risk.

AUBAGIO can increase the plasma concentration of oral contraceptives 1.54-fold, therefore consideration should be given to the type or dose of oral contraceptives used (see DRUG INTERACTIONS).

Use in males
Teriflunomide is detected in human semen. Animal studies to specifically evaluate the risk of male-mediated fetal toxicity have not been conducted. To minimize any possible risk, men not wishing to father a child and their female partners should use reliable contraception. Men wishing to father a child should discontinue use of AUBAGIO and undergo an accelerated elimination procedure to decrease the plasma concentration of teriflunomide to less than 0.02 mg/L.

Skin

No cases of severe skin reactions have been reported with AUBAGIO in the clinical trials. Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, including a fatal case of toxic epidermal necrolysis, have been reported in the postmarketing setting in patients treated with AUBAGIO for MS. 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, AUBAGIO 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), AUBAGIO and any other possibly associated treatment must be discontinued, and an accelerated elimination procedure initiated immediately. In such cases patients should not be re-exposed to AUBAGIO.

New onset of psoriasis (including pustular psoriasis) and worsening of pre-existing psoriasis have been reported during use of teriflunomide. Discontinuation of treatment and initiation of an accelerated elimination procedure may be considered, taking into account the patient's disease and medical history (see ADVERSE REACTIONS, Postmarket Adverse Events).

Special Populations

Pregnant Women

AUBAGIO is contraindicated for pregnant women or women of childbearing age not using reliable contraception (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Reproduction).

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 (see TOXICOLOGY, Teratogenicity).

Women of childbearing potential must not be started on AUBAGIO until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting treatment with AUBAGIO, patients must be fully counseled on the potential for serious risk to the fetus (see WARNINGS AND PRECAUTIONS, Reproduction).

Pregnancy Registry

A pregnancy registry has been established to collect information about the effect of AUBAGIO exposure during pregnancy. Physicians are encouraged to enroll pregnant women in the AUBAGIO pregnancy registry, or pregnant women may enroll themselves in the AUBAGIO pregnancy registry by calling 1-800-745-4447, option 2.

Labour and Delivery

There is no adequate information regarding the effects of AUBAGIO on labour and delivery in pregnant women.

Nursing Women

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.

Pediatrics (< 18 years of age)

The safety and effectiveness of AUBAGIO have not been established in pediatric patients and AUBAGIO is not recommended in this patient population.

Geriatrics (> 65 years of age)
Clinical studies of AUBAGIO did not include patients over 65 years old. AUBAGIO should be used with caution in patients aged 65 years and over. Physicians who choose to treat geriatric patients should consider that treatment with AUBAGIO in the context of a greater frequency of other concomitant diseases and concomitant drug therapy warrants caution and may necessitate additional or more frequent monitoring.

Hepatic Impairment
AUBAGIO is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Hepatic/Pancreatic). Mild and moderate hepatic impairment had no impact on the pharmacokinetics of teriflunomide. No dosage adjustment is anticipated for patients with mild and moderate hepatic impairment.

Renal Impairment
Severe renal impairment had no impact on the pharmacokinetics of teriflunomide. No dosage adjustment is necessary for patients with severe renal impairment.
Patients with severe renal impairment undergoing dialysis were not evaluated. Teriflunomide is not recommended in this population.

Monitoring and laboratory tests

- Check blood pressure before initiation of treatment with AUBAGIO and periodically throughout treatment. Blood pressure should be appropriately managed during treatment with AUBAGIO.
- Obtain a complete blood cell (CBC) count before initiation of treatment with AUBAGIO and periodically during treatment. Further monitoring should be based on signs and symptoms suggestive of infection.
- Obtain serum transaminases and bilirubin levels within 6 months before initiation of treatment with AUBAGIO. Monitor ALT levels at least monthly for at least six months after starting AUBAGIO.
- Obtain a negative pregnancy test before initiation of treatment with AUBAGIO.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following most common adverse reactions were reported with a frequency ≥10% in the 14 mg teriflunomide group and a difference of ≥1% as compared to placebo: alopecia, diarrhea, ALT increased, and nausea.

The safety findings during long-term treatment with AUBAGIO were generally consistent with those reported during the 2-year placebo controlled clinical trials (see ADVERSE REACTIONS, Long-term safety).

Teriflunomide is the main metabolite of leflunomide. The safety profile of leflunomide in patients suffering from rheumatoid arthritis may be pertinent when prescribing teriflunomide in MS patients.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Placebo Controlled Trials

A total of 786 patients on teriflunomide 14 mg once daily and 806 on placebo constituted the safety population in the pooled analysis of placebo controlled studies in patients with relapsing remitting forms of MS (RRMS) (see CLINICAL TRIALS).

Table 1: Adverse Reactions in Placebo controlled studies (occurring in ≥ 1% of patients, and reported for teriflunomide 14 mg at ≥1% higher rate than for placebo)

PRIMARY SYSTEM ORGAN CLASS Preferred Term (%)	Teriflunomide 14 mg (N=786)	Placebo (N=806)
INFECTIONS AND INFESTATIONS		
Influenza	72 (9.2%)	60 (7.4%)
Sinusitis	47 (6.0%)	31 (3.8%)
Gastroenteritis viral	23 (2.9%)	11 (1.4%)
Oral herpes	19 (2.4%)	10 (1.2%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Neutropenia	54 (6.9%)	13 (1.6%)
NERVOUS SYSTEM DISORDERS		
Paraesthesia	66 (8.4%)	57 (7.1%)
Carpal tunnel syndrome	16 (2.0%)	8 (1.0%)
VASCULAR DISORDERS		
Hypertension	33 (4.2%)	16 (2.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Dyspnoea	13 (1.7%)	5 (0.6%)
GASTROINTESTINAL DISORDERS		
Diarrhoea	113 (14.4%)	63 (7.8%)
Nausea	97 (12.3%)	63 (7.8%)
Abdominal pain upper	44 (5.6%)	35 (4.3%)
Toothache	25 (3.2%)	15 (1.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia	111 (14.1%)	35 (4.3%)
Rash	39 (5.0%)	27 (3.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Musculoskeletal pain	28 (3.6%)	19 (2.4%)
RENAL AND URINARY DISORDERS		
Pollakiuria	16 (2.0%)	8 (1.0%)

PRIMARY SYSTEM ORGAN CLASS Preferred Term (%)	Teriflunomide 14 mg (N=786)	Placebo (N=806)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Menorrhagia	12 (1.5%)	3 (0.4%)
INVESTIGATIONS		
Alanine aminotransferase increased	110 (14.0%)	62 (7.7%)
Aspartate aminotransferase increased	24 (3.1%)	10 (1.2%)
Weight decreased	21 (2.7%)	8 (1.0%)
Gamma-glutamyltransferase increased	18 (2.3%)	7 (0.9%)
Neutrophil count decreased	17 (2.2%)	8 (1.0%)
White blood cell count decreased	11 (1.4%)	2 (0.2%)

The most frequently reported (in > 1% of patients treated with AUBAGIO) Treatment Emergent Adverse Events leading to discontinuation are neutropenia 8 (1%), alopecia 12 (1.5%) and alanine aminotransferase increased 14 (1.7%).

Cardiovascular deaths

Four cardiovascular deaths, including three sudden deaths, and one myocardial infarction in a patient with a history of hyperlipidemia and hypertension were reported among approximately 2600 patients exposed to AUBAGIO in the premarketing database. These cardiovascular deaths occurred during uncontrolled extension studies, one to nine years after initiation of treatment. A relationship between teriflunomide and cardiovascular death has not been established.

Hypophosphatemia

In clinical trials, 17% of 14 mg teriflunomide-treated subjects had mild hypophosphatemia (≥ 0.6 mmol/L and < lower limit of normal), compared to 6% of placebo-treated subjects; 5% of 14 mg teriflunomide-treated subjects had moderate hypophosphatemia (≥0.3 mmol/L and <0.6 mmol/L), compared to 1% of placebo-treated subjects. No subject on teriflunomide 14 mg had a serum phosphorus <0.3 mmol/L.

Mean changes from baseline in inorganic phosphorus over time showed an effect of teriflunomide compared to placebo. The decrease in inorganic phosphorus in the teriflunomide groups was apparent as early as Week 2. The mean inorganic phosphorus level with teriflunomide decreased steadily within the first 6 to 12 weeks and stabilized thereafter until the end of the study. At Week 12 the mean changes from baseline in inorganic phosphorus were -0.01 mmol/L, and -0.14 mmol/L on placebo, and 14 mg, respectively.

Alopecia

Alopecia was reported as hair thinning, decreased hair density, hair loss, associated or not with

hair texture change, in 14.6% of patients treated with 14 mg teriflunomide versus 4.5% in patients treated with placebo. Most cases were described as diffuse or generalized over scalp (no complete hair loss reported) and occurred most often during the first 6 months and with resolution in 100 of 115 (87%) patients treated with teriflunomide 14 mg; with almost all cases resolving while on therapy. Discontinuation because of alopecia was 1.5% in the 14 mg teriflunomide group, versus, 0.1% in the placebo group.

Long-term safety

A long term extension of one of the placebo-controlled clinical trials (TEMSO) in patients with RRMS evaluated the safety of teriflunomide in patients treated with teriflunomide for an overall median treatment duration of approximately 5 years (maximum treatment duration approximately 8.5 years). The safety findings during long-term treatment with AUBAGIO were generally consistent with those reported during the 2-year placebo controlled clinical trials (see WARNINGS AND PRECAUTIONS; WARNINGS AND PRECAUTIONS, Monitoring and laboratory tests; ADVERSE REACTIONS, Placebo Controlled Trials).

Post-Market Adverse Events

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

Hypersensitivity reactions (see WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity)

- Immediate or delayed, some of which were severe, such as anaphylaxis and angioedema

Skin and Subcutaneous Tissue Disorders (see WARNINGS AND PRECAUTIONS, Skin)

- Severe skin reactions including toxic epidermal necrolysis and Stevens Johnson syndrome
- Psoriasis (including pustular psoriasis)

Respiratory, thoracic and mediastinal disorders (see WARNINGS AND PRECAUTIONS, Respiratory)

- Interstitial lung disease (ILD)

Gastrointestinal Disorders (see WARNINGS AND PRECAUTIONS, Hepatic/Pancreatic, Skin)

- Stomatitis (such as aphthous or ulcerative)
- Pancreatitis

Hepatobiliary Disorders (see WARNINGS AND PRECAUTIONS, Hepatotoxicity and Risk of Teratogenicity, Hepatic/Pancreatic)

Hepatic Disorders

- Liver failure
- Drug-induced liver injury (DILI)

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

Abnormal Hematologic Findings

In placebo-controlled studies, neutrophil count < $1.5x10^9$/L was observed in 16% of patients on AUBAGIO 14 mg compared with 6% of patients on placebo; lymphocyte count <$0.8x10^9$/L was observed in 11% of patients on AUBAGIO 14 mg compared with 6% of patients on placebo.

Table 2: Abnormal Hematologic Results

	Teriflunomide 14 mg (N=786)	**Placebo (N=806)**
Neutrophil count < $1.5x10^9$/L	125/783 (16%)	48/804 (6%)
Lymphocyte count <$0.8x10^9$/L	88/783 (11%)	48/804 (6%)
Lymphocyte count <$0.5x10^9$/L	19/783 (2.4%)	5/804 (0.6%)

DRUG INTERACTIONS

Overview

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.

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

Caution is recommended if AUBAGIO is used in combination with other hepatotoxic drugs due to a potential for additive hepatotoxic effects or if AUBAGIO is used in patients with a history of drug-induced hepatotoxicity (see WARNINGS AND PRECAUTIONS, Hepatic/Pancreatic; ADVERSE REACTIONS, Post-Market Adverse Events).

Co-administration with antineoplastic or immunosuppressive therapies used for treatment of multiple sclerosis has not been evaluated and is not recommended due to the potential risk of additive immune system effects. Caution should also be exercised when switching patients to or from another agent with a known potential for hematologic suppression because there will be overlap of systemic exposure to both compounds (see WARNINGS AND PRECAUTIONS, Hematologic).

Drug-Drug Interactions

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.

Rifampin did not affect the pharmacokinetics of teriflunomide.

Potential for AUBAGIO to affect other drugs

Table 3 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
CYP2C8 substrates	CT	Increase in drug concentration	There was an increase in mean repaglinide C_{max} and AUC (1.64 - and 2.28-fold, respectively), following repeated doses of teriflunomide and a single dose of 0.25 mg repaglinide, 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.
Oral contraceptives	CT	Increase in drug concentration	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.
CYP1A2 substrates	CT	Decrease in drug concentration	Repeated doses of teriflunomide decreased mean C_{max} 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 duloxetine, theophylline and tizanidine) should be used with caution during treatment with teriflunomide, as it could lead to the reduction of efficacy of these drugs.
Warfarin	CT	Decrease in INR	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.

Proper name	Ref	Effect	Clinical comment
CYP2B6, CYP3A, CYP2C9, CYP2C19 and CYP2D6 substrates	CT	No effect	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).
Organic anion transporter (OAT) 3 substrates	CT	Increase in drug concentration	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, penicillin G, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution should be observed.
BCRP and /or organic anion transporting polypeptide (OATP) 1B1 and 1B3 substrates	CT		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. If used together, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., methotrexate, mitoxantrone, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family, especially HMG-Co reductase inhibitors (e.g., 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.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Food does not have a clinically relevant effect on teriflunomide pharmacokinetics. Therefore, teriflunomide, once daily can be taken with or without food.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Monitoring recommended prior to initiating and during treatment:

- Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for at least six months after starting AUBAGIO (see WARNINGS AND PRECAUTIONS, Hepatic/Pancreatic).
- Obtain a complete blood cell count (CBC) within 6 months before the initiation of treatment with AUBAGIO and periodically during treatment. Further monitoring should be based on signs and symptoms of infection (see WARNINGS AND PRECAUTIONS, Hematologic).
- Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection (see WARNINGS AND PRECAUTIONS, Immune - Infections).
- Check blood pressure before start of AUBAGIO treatment and periodically throughout treatment (see WARNINGS AND PRECAUTIONS, Cardiovascular).
- Obtain a negative pregnancy test before initiation of treatment with AUBAGIO (see WARNINGS AND PRECAUTIONS, Special Populations – Pregnant Women).

Recommended Dose and Dosage Adjustment

The recommended dose of AUBAGIO is 14 mg orally once daily which can be taken with or without food.

Pediatric patients
The safety and effectiveness of AUBAGIO have not been established in pediatric patients and AUBAGIO is not recommended in this patient population.

Geriatric patients
Clinical studies of AUBAGIO did not include patients over 65 years old. AUBAGIO should be used with caution in patients aged 65 years and over due the greater frequency of other concomitant diseases and concomitant drug therapy (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Special Populations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions).

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, WARNINGS AND PRECAUTIONS, Hepatic and Special Populations).

Renal impairment
No dosage adjustment is necessary for patients with severe renal impairment (see WARNINGS AND PRECAUTIONS, Renal and Special Populations – Renal impairment).

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

Missed Dose
If a dose is missed, treatment should be continued with the next dose as planned.

OVERDOSAGE

There is no experience regarding teriflunomide symptomatic overdose or intoxication in humans.

Teriflunomide 70 mg daily up to 14 days was well tolerated by healthy subjects.

In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination (see WARNINGS AND PRECAUTIONS, General, Accelerated Elimination Procedure).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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, may diminish the numbers of activated lymphocytes in peripheral blood. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not known, but may involve reduced numbers of activated lymphocytes available for migration into the central nervous system (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.

Immune system
Effect on antibody response
In a clinical study, teriflunomide-treated patients mounted appropriate immune responses to a seasonal influenza vaccination. Patients achieved post-vaccination antibody titers, consistent with seroprotection. Also, the immunogenicity of rabies vaccine was assessed in a placebo controlled study in healthy volunteers. This study showed that although the antibody levels (mean titers 15.2 IU/mL post vaccination) were well above the threshold for seroprotection (≥0.5 IU/mL) the immunologic response was decreased during treatment with AUBAGIO. Compared to placebo, antibody titers in response to rabies vaccine were 47% lower in subjects receiving AUBAGIO.

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 10^9/L, which occurred over the first 3 months of treatment; these reductions were maintained until the end of the treatment.

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.

Pharmacokinetics

Teriflunomide is the main active metabolite of leflunomide and is responsible for leflunomide's activity *in vivo*. At recommended doses, teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide.

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

Absorption: Median time to reach maximum plasma concentrations occurs between 1 to 4 hours post-dose following oral administration of teriflunomide.

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.

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.

Excretion: Teriflunomide was excreted in the gastrointestinal tract mainly through the bile as unchanged drug and possibly by direct secretion. The metabolites of teriflunomide are mainly excreted by the kidneys. Over 21 days, 60.1% of the administered dose was 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 was 30.5 mL/h.

Accelerated Elimination Procedure: Cholestyramine and activated charcoal

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mg/L, but because of 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 (see WARNINGS AND PRECAUTIONS, General, Accelerated Elimination Procedure). Use of the accelerated elimination procedure may potentially result in a gradual return of disease activity if the patient had been responding to AUBAGIO treatment.

Special Populations and Conditions

Pediatrics:

The safety and effectiveness of AUBAGIO have not been established in pediatric patients and AUBAGIO is not recommended in this patient population.

A population pharmacokinetic model was developed to describe the pharmacokinetics of teriflunomide in 135 pediatric patients with RRMS (10 to 17 years) once daily dosing.

Allometric scaling by body weight was used to describe the changes in the apparent oral clearance and distribution volumes of teriflunomide in the pediatric subjects. Overall exposures in pediatric patients weighing more than 40 kg were within the range of exposures in adult patients with RMS after 14 mg once daily; however the median steady state AUC_{0-24} and Cmax were about 17% higher. Six out of the 102 pediatric patients weighing more than 40 kg reached adult exposure levels with a 7 mg daily dose. Pharmacokinetic modelling predicts that if these patients would have received 14mg daily, their exposure would still have been within the range of exposures seen in adults treated with 14 mg daily.There is limited experience in pediatric patients with body weight below 40 kg.

Median $t_{1/2z}$ was approximately 20 days. Steady-state is estimated to be reached approximately after 3 months.

Geriatrics: The pharmacokinetics in patients aged 65 and over has not been studied. AUBAGIO should be used with caution in patients aged 65 years and over.

Body weight and gender: No dosage adjustment is necessary based on body weight and gender. In a population pharmacokinetic analysis, body weight and gender had a limited impact on AUBAGIO pharmacokinetics (≤35% increase in mean steady-state AUC0-24).

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 has not been evaluated. However, teriflunomide is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Hepatic/Pancreatic and Special Populations).

Renal impairment

Severe renal impairment had no impact on the pharmacokinetic of teriflunomide. Therefore no dose adjustment is anticipated in severe renal impaired patients (WARNINGS AND PRECAUTIONS, Renal and Special Populations).

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

Patients with early RRMS
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. Patients were required to have had a first clinical event consistent with acute demyelination, which occurred within 90 days of randomization, with two or more T2 lesions of at least 3 mm diameter that were characteristic of multiple sclerosis. A total of 618 patients were randomized to receive 7 mg (n=205) or 14 mg (n=216) of teriflunomide or placebo (n=197). Patients had a mean age of 32 years, EDSS at baseline of 1.7, and mean disease duration of two months. The primary endpoint was time to a second clinical episode (relapse). The risk of a second clinical attack over two years was statistically significantly less in the teriflunomide 14 mg treatment group compared to the placebo group. The impact of early treatment with AUBAGIO on the long term evolution of the disease in this patient population is not known. Adverse events in this study were quantitatively and qualitatively similar to those reported in the clinical trials with patients diagnosed with more advanced RRMS (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS).

STORAGE AND STABILITY

Store at 15°C to 30°C.

For blister card wallet, remove tablet only when ready to use.

For bottle container, discard after 90 days once opened.

AUBAGIO must be kept out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AUBAGIO is available in film-coated tablets containing 14 mg of teriflunomide: pale blue to pastel blue, pentagonal film-coated tablets with dose strength imprint on one side given as number 14 and engraved with corporate logo on the other side.

Nonmedicinal ingredients: lactose monohydrate, corn starch, hydroxypropylcellulose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating for the 14 mg tablet is made of hypromellose, titanium dioxide, talc, polyethylene glycol and indigo carmine aluminum lake.

AUBAGIO is supplied as:

- Carton of 14 tablets of 14 mg containing 1 wallet composed of 1 folded blister card of 14 tablets per blister card
- Carton of 28 tablets of 14 mg containing 1 wallet composed of 2 folded blister cards of 14 tablets per blister card
- Carton of 84 tablets of 14 mg containing 3 wallets of 28 tablets, each composed of 2 folded blister cards of 14 tablets per blister card
- Bottles of 90 tablets of 14 mg.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

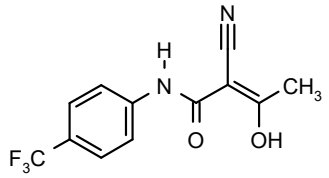
Proper name: teriflunomide

Chemical name: (Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl)-amide

Molecular formula: $C_{12}H_9F_3N_2O_2$

Molecular mass: 270.21

Structural formula:



Physicochemical properties: 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.

CLINICAL TRIALS

The efficacy of AUBAGIO was established in two Phase 3, placebo-controlled studies in patients with relapsing remitting MS.

STUDY 1

Study 1 (TEMSO: Teriflunomide Multiple Sclerosis Oral trial) was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg primarily in patients with relapsing remitting multiple sclerosis (RRMS) over 108 weeks.

Study demographics and trial design

Table 4 – Summary of patient demographics in TEMSO trial

Study	Trial design	Dosage, route of administration and duration	Randomized study subjects (n=number)	Mean age (range)	Gender
TEMSO	Randomized, double-blind, placebo-controlled, parallel-group	Teriflunomide 7 mg or 14 mg, or placebo, once daily for 108 weeks	• Teriflunomide 14 mg: n= 359 • Teriflunomide 7 mg: n=366 • Placebo: n= 363	37.9 (18-55)	F: 72.2% M: 27.8%

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 median age of the study population was 38 years, the median disease duration was 6.83 years, and the median EDSS at baseline was 2.50. A total of 91.4% had relapsing remitting MS (RRMS) and 8.6% had a progressive form of MS with relapses. The median time on treatment was 756 days for placebo and for AUGABIO 14 mg.

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). The key secondary efficacy variable was confirmed progression of disability for at least 12 weeks. The key prespecified MRI endpoint was total lesion volume (defined as sum of T2 and hypointense T1 lesion volume in mL).

Study results
The ARR was significantly reduced in patients treated with 14 mg of AUBAGIO compared to patients who received placebo (ARR: 0.369; p=0.0005 in the 14 mg groups) (Table 5).

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 5 and Figure 1). The estimated percentage of patients with a 12-week sustained disability progression at Week 108 was 27.3%, and 20.2% in the placebo and the 14 mg teriflunomide groups, respectively.

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 lower in the 14 mg group than in the placebo group. Patients in the teriflunomide group had fewer gadolinium- enhancing lesions per T1-weighted scan than those in the placebo group (Table 5).

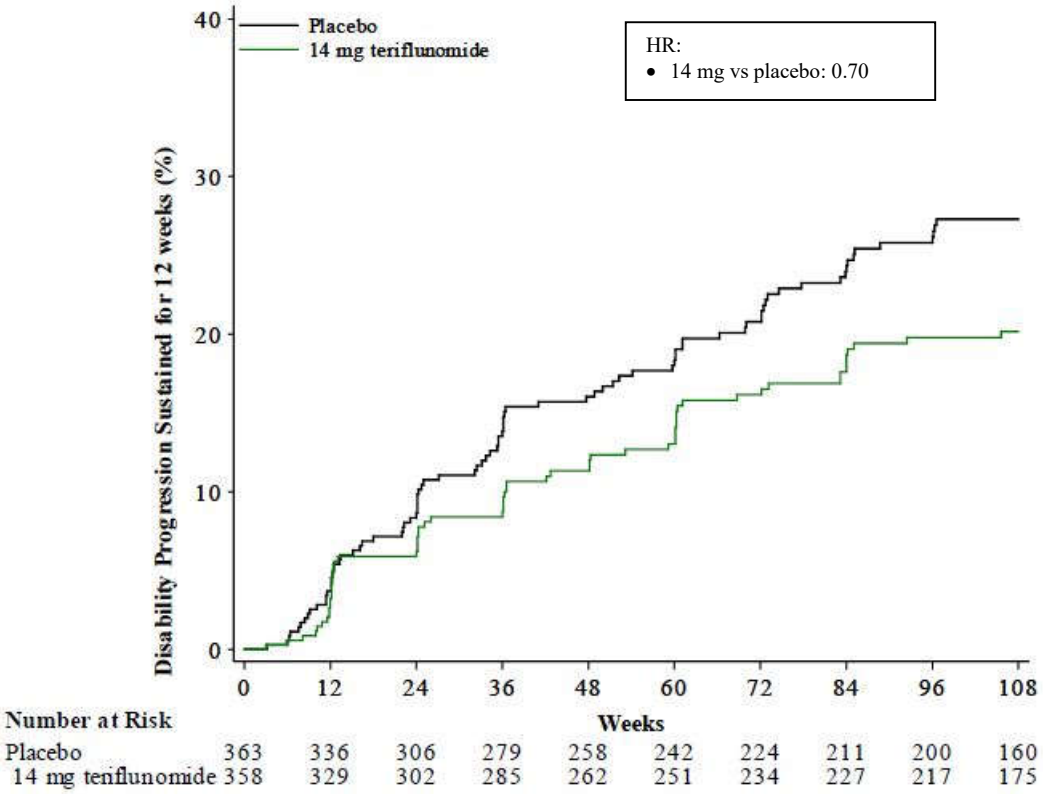
The results for this study are shown in Table 5 and Figure 1:

Table 5- Clinical and MRI Results of TEMSO Study

	Teriflunomide 14 mg N=358	**Placebo N=363**
Clinical Endpoints		
Annualized relapse rate (primary endpoint)	0.369 (p = 0.0005)	0.539
Relative risk reduction	31.5%	
Percent disability progression at week 108[1]	20.2%	27.3%
Hazard ratio	0.70	
Relative risk reduction	30%	
Percent of patients remaining relapse-free at week 108[1]	56.5%	45.6%
MRI Endpoints		
Median change from baseline in Total lesion volume[2] (mL) at week 108	0.345	1.127
Percent change relative to placebo	69%	
Mean number of Gd-enhancing T1-lesions per scan	0.261	1.331
Relative reduction	80%	

[1] Values derived from Kaplan-Meier estimates
[2]Total lesion volume: sum of T2 and hypointense T1 lesion volume in mL

Figure 1 - Kaplan-Meier plot of time to disability progression sustained for 12 weeks - ITT population (Study 1)



STUDY 2

Study 2 (TOWER: Teriflunomide Oral in People With Relapsing Remitting Multiple Sclerosis) was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg in patients with relapsing remitting multiple sclerosis (RRMS) with mean treatment duration of approximately 18 months.

Study demographics and trial design

Table 6 – Summary of patient demographics in TOWER trial

Study	Trial design	Dosage, route of administration and duration	Randomized study subjects (n=number)	Mean age (range)	Gender
TOWER	Randomized, double-blind, parallel group, placebo-controlled study	Teriflunomide 7 mg or 14 mg, or placebo, once daily, up to a fixed end for all patients 48 weeks after the last patient randomized	• Teriflunomide 14 mg: n= 372 • Teriflunomide 7 mg: n=408 • Placebo: n=389	37.9 (18-56)	F: 71.1% M: 28.9%

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, every 12 weeks until completion and at unscheduled visits for suspected relapse.

The primary endpoint was the annualized relapse rate (ARR). The key secondary objective was to assess the effect of the two doses of teriflunomide in comparison to placebo, on disability progression.

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 median age was 38 years and the study population was primarily Caucasian (82.1%) and Asian/Oriental (14.5%). The median time since first diagnosis of MS was 6.25 years, a majority of the patients had relapsing remitting MS (97.5%), and the median number of relapses within the past one year was 1.0. Median EDSS at baseline was 2.50.

Study results

The ARR was significantly reduced in patients treated with 14 mg of AUBAGIO compared to patients who received placebo (ARR: 0.319; p=0.0001 in the 14 mg groups) (Table 7).

The risk of disability progression sustained for 12 weeks (as measured by at least a 1-point increase from baseline EDSS $\leq$ 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

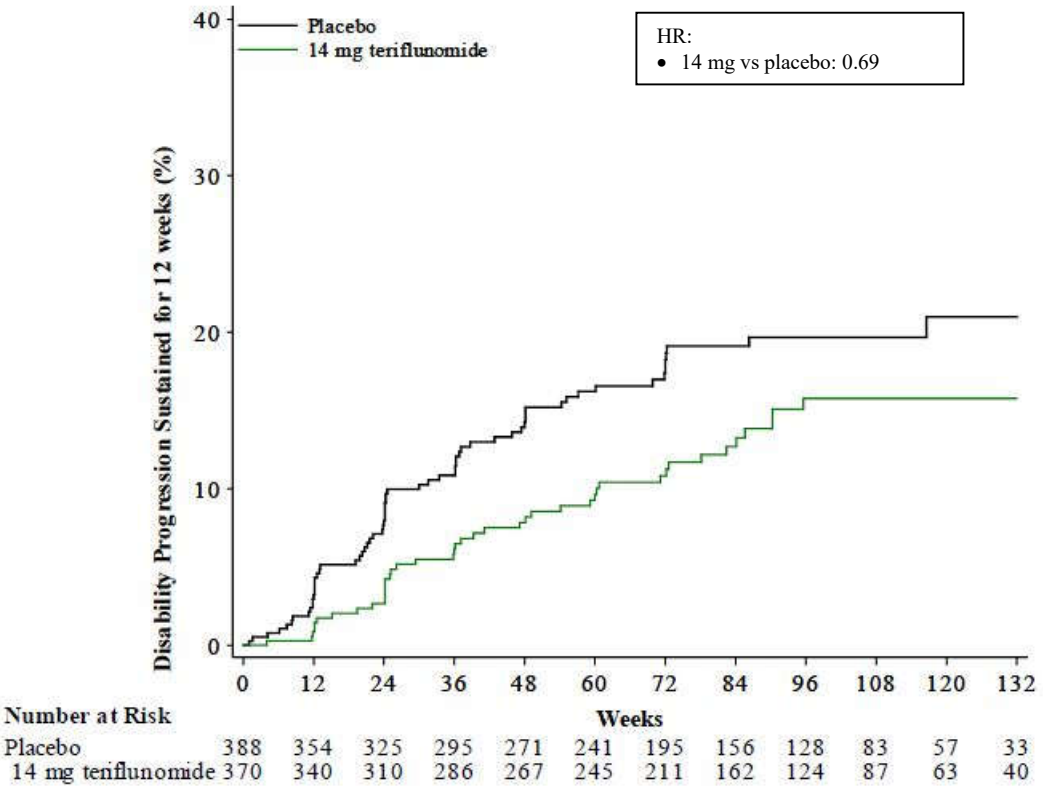
placebo (Table 7 and Figure 2). The estimated percentage of patients with a 12-week sustained disability progression at Week 108 was 19.7%, and 15.8% in the placebo and the 14 mg teriflunomide groups, respectively.

Table 7 - - Clinical Results of TOWER Study

	Teriflunomide 14 mg N=370	**Placebo N=388**
Clinical Endpoints		
Annualized relapse rate (primary endpoint)	0.319 (p = 0.0001)	0.501
Relative risk reduction	36.3%	
Percent of patients remaining relapse-free at week 108[1]	57.1%	46.8%
Percent disability progression at week 108[1]	15.8%	19.7%
Hazard ratio	0.69	
Relative risk reduction	31%	

[1] Values derived from Kaplan-Meier estimates

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



TOXICOLOGY

Carcinogenesis

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 AUC_{0-24}). 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 AUC_{0-24}).

Mutagenesis

Teriflunomide was not mutagenic, in the *in vitro* bacterial reverse mutation (Ames) and hypoxanthine-guanine-phosphoribosyl transferase (HPRT) tests. Teriflunomide was positive in an *in vitro* chromosomal aberration assay in human lymphocytes, with and without metabolic activation. Addition of uridine (to supplement the pyrimidine pool) reduced the magnitude of the clastogenic effect; however, teriflunomide was positive in the *in vitro* chromosomal aberration assay, even in the presence of uridine.

4-Trifluoromethylaniline (4-TFMA), a minor metabolite of teriflunomide, was mutagenic in the Ames and HPRT tests. 4-TFMA was positive in the *in vitro* chromosomal aberration assay in mammalian cells but negative in *in vivo* micronucleus and chromosomal aberration assays.

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 (to supplement the pyrimidine pool) 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.

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.

Teratogenicity

In studies conducted in pregnant rats and rabbits, oral administration of teriflunomide resulted in embryolethality, reduced fetal body weight, and/or malformations. 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 on a mg/kg basis. 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 on a mg/kg basis. 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 teriflunomide was administered to pregnant rats during gestation and lactation, teriflunomide 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 teriflunomide was administered at 1.0 mg/kg/day during the gestation period and not during lactation to avoid transfer of teriflunomide 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 teriflunomide 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 recommended human dose (RHD) on a mg/m^2 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.

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PART III: CONSUMER INFORMATION

AUBAGIO®
Teriflunomide tablets

This leaflet is part III of a three-part "Product Monograph" published when AUBAGIO was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AUBAGIO. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
AUBAGIO is used to treat adult patients with relapsing remitting multiple sclerosis (RRMS).

What it does:
AUBAGIO can alter the way the body's immune system works. AUBAGIO does not cure RRMS, but it can help decrease the number of attacks (relapses) that occur. AUBAGIO can help slow the build-up of physical problems (disability progression) that RRMS causes.

When it should not be used:
Do not take AUBAGIO if you:

- are allergic to teriflunomide, leflunomide or to any of the other ingredients in the formulation
- are taking a drug for rheumatoid arthritis with the medicinal ingredient leflunomide
- have severe liver problems
- have an infection
- are pregnant, suspect you may be pregnant or plan to get pregnant
- are a woman of childbearing potential not using reliable methods of birth control.
- are of childbearing age, until it is confirmed with a pregnancy test that you are not pregnant. This is done just before you begin treatment with AUBAGIO.
- have low platelets, low white blood cell counts, or uncontrolled infection. Low white blood cell counts may be caused by other things that affect the immune system such as:
    - immunodeficiency syndrome or AIDS
    - weakened bone marrow function or transplantation
    - treatments that can suppress the immune system such as
        - drugs used to treat cancer
        - other drugs used to treat MS

What the medicinal ingredient is: teriflunomide

What the nonmedicinal ingredients are:
corn starch, hydroxypropylcellulose, hypromellose, indigo carmine aluminum lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, and titanium dioxide.

What dosage forms it comes in:
Tablet 14 mg

WARNINGS AND PRECAUTIONS

LIVER DISORDER

BIRTH CONTROL, PREGNANCY and RISK OF BIRTH DEFECTS

Liver disorder
AUBAGIO may cause liver disorders. Severe liver injury including fatal liver failure occurred rarely in patients treated with AUBAGIO. The risk for severe liver disorder may be increased if you take AUBAGIO when you already have liver disease or if you are taking other drugs that affect the liver.

Your doctor should do blood tests to check your liver function:
• within 6 months before you start taking AUBAGIO.
• every month, for at least 6 months after you start taking AUBAGIO.

Call your doctor right away if you experience any symptoms of liver disorder.

Birth control, Pregnancy and Risk of Birth Defects
Do not take AUBAGIO if you are pregnant. If used during pregnancy, AUBAGIO may cause major birth defects and even death to your baby. Pregnancy must be avoided by using effective birth control when a man or woman is on AUBAGIO. Continue birth control for two years after you stop taking AUBAGIO to make sure your blood levels of AUBAGIO are low enough. Your doctor can prescribe a medicine to help lower your blood levels of AUBAGIO more quickly. Your doctor can inform you when it is safe to get pregnant or to father a child.

If you are a **woman** of childbearing age, you should have a pregnancy test before you start taking AUBAGIO. If you become pregnant, are late starting your period or have any reason to suspect pregnancy while taking AUBAGIO or within 2 years after stopping it, tell your doctor right away.

Before you take AUBAGIO, tell your doctor or pharmacist about all your medical conditions, including if you:

- have liver problems
- have high blood pressure
- have a fever or infection, or you are unable to fight infections
- had or now have blood or bone marrow problems
- have kidney problems
- had or now have tuberculosis
- have diabetes
- are older than 60 years
- are pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed. It is not known if AUBAGIO passes into your breast milk. You and your doctor should decide if you will take AUBAGIO or breastfeed. You should not do both at the same time.
- have a condition that affects the skin or nails called psoriasis
- have an allergy to lactose or a rare hereditary problem of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption

You should not receive certain types of vaccines (called "live attenuated vaccines") during treatment with AUBAGIO. Check with your doctor before receiving any vaccination during treatment or after stopping AUBAGIO.

Pregnancy Registry: If you become pregnant while taking AUBAGIO or after you stop taking AUBAGIO, talk to your doctor about enrolling in the AUBAGIO Pregnancy Registry at 1-800-745-4447, option 2. The purpose of this registry is to collect information about the effect of AUBAGIO exposure during pregnancy.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with AUBAGIO:

- leflunomide, a medication for rheumatoid arthritis
- medicines that could raise your chance of getting infections, such as medicines to treat cancer or to control your immune system. **Ask your doctor or pharmacist for a list of these medicines if you are not sure**
- warfarin
- medicines used to treat diabetes, such as: repaglinide, pioglitazone, rosiglitazone, nateglinide
- oral contraceptives
- some medicines used to treat infections such as: cefaclor, penicillin G, ciprofloxacin, rifampin, zidovudine
- medicines used to lower blood cholesterol, such as: rosuvastatin, atorvastatin, simvastatin, pravastatin
- anti-inflammatory drugs, such as: indomethacin, ketoprofen, sulfasalazine
- diuretics (water losing pills), such as: furosemide
- some medicines to treat cancer such as: paclitaxel, methotrexate, mitoxantrone, topotecan, daunorubicin, doxorubicin
- duloxetine (anti-depressant); theophylline (asthma medicine); cimetidine (stomach acid medicine); tizanidine (muscle relaxant medicine)
- avoid drinking alcohol while taking AUBAGIO as it may cause liver problems.
- other medicines that can potentially harm the liver

PROPER USE OF THIS MEDICATION

- Follow your doctor's instructions carefully. Do not take more than the recommended dose.
- Take AUBAGIO orally (by mouth) with or without food.
- Do not stop taking AUBAGIO without talking with your doctor first.

Usual Adult Dose: 1 tablet a day.

Missed dose:
If you missed a dose, take just the next following dose. Do not take a double dose to make up for a forgotten tablet.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- diarrhea, nausea, flu or sinus infection, upset stomach, abdominal pain
- rash
- abnormal liver tests
- hair thinning or loss

If any of these affects you severely, tell your doctor, nurse or pharmacist.

AUBAGIO can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Deaths due to heart-related issues have occurred in patients treated with AUBAGIO.

AUBAGIO may cause or worsen a condition that affects the skin or nails, called psoriasis.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Decreased White Blood Cells:** infections, feeling unusually tired, fever, aches, pains and flu-like symptoms		√	
	High Blood Pressure: headaches, vision disorders, nausea and vomiting		√	
	Liver Disorder: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, weight loss, unusual tiredness.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Uncommon	**Heart Attacks:** shortness of breath, chest pain,feeling of a rapid heart beat, light headedness, nausea, vomiting, anxiety			√
	Decreased Platelets: bruising, bleeding, feeling unusually tired and weakness		√	
	Peripheral Neuropathy/ Carpal tunnel syndrome: numbness or tingling of hands or feet		√	
Rare	**Interstitial Lung Disease:** shortness of breath, trouble breathing, lasting cough		√	
Unknown	**Allergic/ Hypersensitivity reaction** Rash, itching, trouble breathing, swelling of the face, lips tongue or throat			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
Unknown	**Pancreatitis** Severe pain in upper abdominal area which may spread to back, nausea, vomiting, fever			√
	Severe Skin Reactions: **Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis:** any combination of itchy skin rash, redness, blistering and peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, with fever, chills, headache, cough, body aches or swollen glands, joint pain, yellowing of the skin or eyes, dark urine.			√

This is not a complete list of side effects. For any unexpected effects while taking AUBAGIO, contact your doctor or pharmacist.

HOW TO STORE IT

Store AUBAGIO between 15° to 30°C.

For blister card wallet, remove tablet only when ready to use.

Once the bottle is opened, the tablets must be used within 90 days.

Keep AUBAGIO and all medicines out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at www.sanofi.ca or by contacting the sponsor, Sanofi Genzyme, a division of Sanofi-aventis Canada Inc. at: 1-855-671-2663

This leaflet was prepared by Sanofi Genzyme, a division of sanofi-aventis Canada Inc.

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