

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202992Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AUBAGIO® safely and effectively. See full prescribing information for AUBAGIO.

AUBAGIO (teriflunomide) tablets for oral administration.
Initial U.S. Approval: 2012

WARNING: HEPATOTOXICITY and RISK OF TERATOGENICITY
See full prescribing information for complete boxed warning

Hepatotoxicity

Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO and monitor ALT levels at least monthly for six months (5.1). If drug induced liver injury is suspected, discontinue AUBAGIO and start accelerated elimination procedure (5.3).

Risk of Teratogenicity

Based on animal data, AUBAGIO may cause major birth defects if used during pregnancy. AUBAGIO is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during AUBAGIO treatment. (4.2, 5.2)

INDICATIONS AND USAGE

AUBAGIO is a pyrimidine synthesis inhibitor indicated for the treatment of patients with relapsing forms of multiple sclerosis (1)

DOSAGE AND ADMINISTRATION

7 mg or 14 mg orally once daily, with or without food. (2)

DOSAGE FORMS AND STRENGTHS

7 mg and 14 mg film-coated tablets (3)

CONTRAINDICATIONS

- Severe hepatic impairment (4.1, 5.1)
- Pregnancy (4.2, 5.2, 8.1)
- Current leflunomide treatment (4.3)

WARNINGS AND PRECAUTIONS

- Elimination of AUBAGIO can be accelerated by administration of cholestyramine or activated charcoal for 11 days (5.3)
- AUBAGIO may decrease WBC. A recent CBC should be available before starting AUBAGIO. Monitor for signs and symptoms of infection. Consider suspending treatment with AUBAGIO and using accelerated elimination procedure in case of serious infection. Do not start AUBAGIO in patients with active infections (5.4)
- Peripheral neuropathy: If patient develops symptoms consistent with peripheral neuropathy, evaluate patient and consider discontinuing AUBAGIO and using accelerated elimination procedure (5.5)
- Acute renal failure/hyperkalemia: Monitor renal function and potassium in patients with symptoms of renal failure or hyperkalemia (5.6, 5.7)
- Severe skin reaction: Stop AUBAGIO and use accelerated elimination procedure (5.8)
- Blood pressure: Measure at treatment initiation. Monitor and manage appropriately during treatment (5.9)

ADVERSE REACTIONS

Most common adverse reactions (≥10% and ≥2% greater than placebo): ALT increased, alopecia, diarrhea, influenza, nausea, and paresthesia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs metabolized by CYP2C8: Monitor patients as teriflunomide may increase their exposure (7)
- Teriflunomide may increase exposure of ethinylestradiol and levonorgestrel. Choose an appropriate oral contraceptive (7)
- Drugs metabolized by CYP1A2: Monitor patients as teriflunomide may decrease their exposure (7)
- Warfarin: monitor INR as teriflunomide may decrease INR (7)

USE IN SPECIFIC POPULATIONS

- Contraindicated in pregnancy; pregnancy registry available (4.2, 8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2012

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FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY and RISK OF TERATOGENICITY

Hepatotoxicity

Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. 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 six months after starting AUBAGIO [see *Warnings and Precautions (5.1)*]. If drug induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or charcoal [see *Warnings and Precautions (5.3)*]. AUBAGIO is contraindicated in patients with severe hepatic impairment [see *Contraindications (4.1)*]. 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 (4.2)*, *Warnings and Precautions (5.2)*, and *Use in Specific Populations (8.1)*].

1. INDICATIONS AND USAGE

AUBAGIO[®] is indicated for the treatment of patients with relapsing forms of multiple sclerosis [see *Clinical Studies (14)*].

2. DOSAGE AND ADMINISTRATION

The recommended dose of AUBAGIO is 7 mg or 14 mg orally once daily. AUBAGIO can be taken with or without food.

Monitoring to assess safety

- Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO [see *Warnings and Precautions (5.1)*].
- Obtain a complete blood cell count (CBC) within 6 months before the initiation of treatment with AUBAGIO. Further monitoring should be based on signs and symptoms of infection [see *Warnings and Precautions (5.4)*].

- Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection with a tuberculin skin test [*see Warnings and Precautions (5.4)*].
- Check blood pressure before start of AUBAGIO treatment and periodically thereafter [*see Warnings and Precautions (5.10)*].

3. DOSAGE FORMS AND STRENGTHS

AUBAGIO is available as 7 mg and 14 mg tablets.

The 14 mg tablet is a pale blue to pastel blue, pentagonal film-coated tablet with the dose strength, “14” imprinted on one side and engraved with the corporate logo on the other side. Each tablet contains 14 mg of teriflunomide.

The 7 mg tablet is a very light greenish-bluish grey to pale greenish-blue, hexagonal film-coated tablet with dose strength “7” imprinted on one side and engraved with the corporate logo on other side. Each tablet contains 7 mg of teriflunomide.

4. CONTRAINDICATIONS

4.1. Severe Hepatic Impairment

Patients with severe hepatic impairment [*see Warnings and Precautions (5.1)*].

4.2 Patients Who are Pregnant or Women of Childbearing Potential Not Using Reliable Contraception

AUBAGIO may cause fetal harm when administered to a pregnant woman.

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. Nonclinical studies indicate further that the intended pharmacologic action of the drug is involved in the mechanism of developmental toxicity [*see Use in Specific Populations (8.1)*].

AUBAGIO is contraindicated in women who are pregnant or women of child bearing potential not using reliable contraception. If this drug is used during pregnancy, or 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 (5.3)*]. Under these conditions, the patient should be referred to an obstetrician/gynecologist, preferably experienced in reproductive toxicity, for further evaluation and counseling. [*See Warnings and Precautions and Use in Specific Populations (5.2, 8.1)*]

4.3. Current treatment with leflunomide

Co-administration of teriflunomide with leflunomide is contraindicated.

5. WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Severe liver injury including fatal liver failure and dysfunction has been reported in some patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. 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 (4)*].

In placebo-controlled trials, ALT greater than three times the ULN occurred in 14/429 (3%) and 21/415 (5%) of patients on teriflunomide 7 mg and 14 mg, respectively, and 17/421 (4%) of patients on placebo, during the treatment period. These elevations occurred mostly within the first year of treatment. Half of the cases returned to normal without drug discontinuation. In clinical trials, if ALT elevation was greater than three times the ULN on two consecutive tests, AUBAGIO was discontinued and patients underwent an accelerated elimination procedure [see *Warnings and Precautions (5.3)*]. Of the patients who underwent discontinuation and accelerated elimination in controlled trials, half returned to normal or near normal values within 2 months.

One patient in the controlled trials 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. Teriflunomide-induced liver injury in this patient could not be ruled out.

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 additional monitoring when AUBAGIO is given with other potentially hepatotoxic drugs. 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. If liver injury is suspected to be AUBAGIO-induced, discontinue teriflunomide and start an accelerated elimination procedure [see *Warnings and Precautions (5.3)*] 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.

5.2 Use in Women of Childbearing Potential

There are no adequate and well-controlled studies evaluating AUBAGIO in pregnant women. However, based on animal studies, teriflunomide may increase the risk of teratogenic effects or fetal death when administered to a pregnant woman [see *Contraindications (4.2)*].

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. 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. It is possible that rapidly lowering the plasma concentration of teriflunomide by instituting an accelerated elimination procedure may decrease the risk to the fetus from AUBAGIO [see *Warnings and Precautions (5.3)*].

Upon discontinuing AUBAGIO, it is recommended that all women of childbearing potential 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 of teriflunomide plasma concentrations less than 0.02 mg/L (0.02 mcg/mL). Human plasma concentrations of teriflunomide less than 0.02 mg/L (0.02 mcg/mL) are expected to have minimal risk. [see *Contraindications (4.2)*, *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.1)*]

5.3 Procedure for Accelerated Elimination of Teriflunomide

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, although 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. 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.

5.4 Bone Marrow Effects/Immunosuppression Potential/Infections

White Blood Cell (WBC) count decrease

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. The decrease in mean WBC count occurred during the first 6 weeks and WBC count remained low during treatment. In placebo-controlled studies, neutrophil count $< 1.5 \times 10^9/L$ was observed in 10% and 15% of patients on AUBAGIO 7

mg and 14 mg, respectively, compared with 5% of patients on placebo; lymphocyte count $<0.8 \times 10^9/L$ was observed in 7% and 10% of patients on AUBAGIO 7 mg and 14 mg, respectively, compared with 5% of patients on placebo. No cases of serious pancytopenia were reported in premarketing clinical trials of AUBAGIO but rare cases of pancytopenia, agranulocytosis, and thrombocytopenia have been reported in the postmarketing setting with leflunomide. A similar risk would be expected for teriflunomide [see *Clinical Pharmacology* (12.3)]. Obtain a complete blood cell count (CBC) within 6 months before the initiation of treatment with AUBAGIO. Further monitoring should be based on signs and symptoms suggestive of bone marrow suppression.

Risk of Infection / Tuberculosis Screening

Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved. If a patient develops a serious infection consider suspending treatment with AUBAGIO and using an 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 not recommended for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections. Medications like teriflunomide that have immunosuppression 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 7 mg (1.4%) or 14 mg (2.2%) compared to placebo (2.1%). However, one fatal case of klebsiella pneumonia sepsis occurred in a patient taking teriflunomide 14 mg for 1.7 years. Fatal infections have been reported in the post-marketing setting, in patients receiving leflunomide, especially *Pneumocystis jiroveci* pneumonia and aspergillosis. 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, cytomegalovirus hepatitis reactivation has been observed.

In clinical studies with AUBAGIO, cases of tuberculosis have been observed. Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection with a tuberculin skin test. AUBAGIO has not been studied in patients with a positive tuberculosis screen, and the safety of AUBAGIO in individuals with latent tuberculosis infection is unknown. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with AUBAGIO.

Vaccination

No clinical data are available on the efficacy and safety of 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.

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppressive medications. There is a potential for immunosuppression with teriflunomide. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the AUBAGIO clinical trials, but larger and longer-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with AUBAGIO.

5.5 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 AUBAGIO than in patients taking placebo. In one 108-week placebo-controlled study in 1086 patients with multiple sclerosis, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.2% (4 patients) and 1.9% (6 patients) on 7 mg and 14 mg of AUBAGIO, respectively, compared with 0% on placebo. Treatment was discontinued in 2 patients with polyneuropathy, one on each dose; one of them recovered following treatment discontinuation. The other cases 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 [see *Warnings and Precautions* (5.3)].

5.6 Acute Renal Failure

In placebo-controlled trials, 10 of 844 (1.2%) of AUBAGIO-treated subjects had transient acute renal failure with a creatinine measurement increased by 100% or more of their baseline serum creatinine value, compared to 0 of 421 placebo-treated subjects. Seven of the 10 subjects had a nadir creatinine clearance less than 30 cc/minute. In each of the 10 subjects, the serum creatinine level was normal on the next reported measurement (6-48 days from the increase in creatinine) with continued teriflunomide use. These increased creatinine measurements occurred between 12 weeks and 2 years after first dose of teriflunomide. Of the 6 subjects with available serum potassium measurements, 3 (50%) had hyperkalemia (measurements of 6.7, >7.3, and >7.3 mmol/L). No associated symptoms were documented.

AUBAGIO causes increases in renal uric acid clearance with mean decreases in serum uric acid of 20-30%. Acute uric acid nephropathy is a likely explanation for the cases of transient acute renal failure seen with teriflunomide. Although symptoms associated with acute uric acid nephropathy, such as loin pain or flank pain, were not reported, this information was not systematically collected. No inciting factors, such as dehydration, exercise, or increase in physical activity in the 30 days prior to the adverse event were reported, but this information was not systematically collected.

5.7 Hyperkalemia

In placebo-controlled trials, treatment-emergent hyperkalemia >7.0 mmol/L occurred in 8/829 (1.0%) of teriflunomide-treated subjects, compared to 1/414 (0.2%) of placebo-treated subjects. Two teriflunomide-treated subjects had hyperkalemia >7.0 mmol/L with acute renal failure. Possible causes in other cases were not documented. Check serum potassium level in AUBAGIO-treated patients with symptoms of hyperkalemia or with acute renal failure.

5.8 Skin Reactions

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients with rheumatoid arthritis receiving leflunomide. A similar risk would be expected for teriflunomide [see Clinical Pharmacology (12.3)]. If a patient taking AUBAGIO develops any of these conditions, stop AUBAGIO therapy and perform an accelerated elimination procedure [see *Warnings and Precautions* (5.3)].

5.9 Blood Pressure Increase

In placebo-controlled studies, mean change from baseline in systolic blood pressure was 2.9 mmHg and 2.7 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -1.3 mmHg for placebo. The change from baseline in diastolic blood pressure was 1.4 mmHg and 1.3 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -0.9 mmHg for placebo. Hypertension was reported as an adverse reaction in 4% of patients treated with 7 mg or 14 mg of AUBAGIO, compared with 2% on placebo. Check blood pressure before start of AUBAGIO treatment and periodically thereafter. Elevated blood pressure should be appropriately managed during treatment with AUBAGIO.

5.10 Respiratory Effects

Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during treatment with leflunomide. A similar risk would be expected for teriflunomide [see Clinical Pharmacology (12.3)]. Interstitial lung disease may be fatal. Interstitial lung disease may occur acutely at any time during therapy and has a variable clinical presentation. 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 [see *Warnings and Precautions* (5.3)].

5.11 Concomitant Use with Immunosuppressive or Immunomodulating Therapies

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.

In any situation in which the decision is made to switch from AUBAGIO to another agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. Use of an accelerated elimination procedure may decrease this risk, but may also potentially result in return

of disease activity if the patient had been responding to AUBAGIO treatment [see *Warnings and Precautions (5.3)*].

6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the prescribing information:

- Hepatotoxicity [see *Contraindications (4.1) and Warnings and Precautions (5.1)*]
- Bone Marrow Effects/Immunosuppression Potential/Infections [see *Warnings and Precautions (5.4)*]
- Peripheral Neuropathy [see *Warnings and Precautions (5.5)*]
- Acute Renal Failure [see *Warnings and Precautions (5.6)*]
- Hyperkalemia [see *Warnings and Precautions (5.7)*]
- Serious Skin Reactions [see *Warnings and Precautions (5.8)*]
- Blood Pressure Effects [see *Warnings and Precautions (5.9)*]
- Respiratory Effects [see *Warnings and Precautions (5.10)*]

The most frequent adverse reactions for AUBAGIO (incidence $\geq 10\%$ and $\geq 2\%$ greater than placebo) in the placebo-controlled studies were ALT increased, alopecia, diarrhea, influenza, nausea, and paresthesia. Alopecia was the most common cause of discontinuation because of adverse events in controlled clinical studies as compared to placebo (0.5% and 1.4% of patients on AUBAGIO 7 mg and 14 mg, respectively, and 0% on placebo).

If desired, teriflunomide can be rapidly cleared from the body by the use of an accelerated elimination procedure [see *Warnings and Precautions (5.3)*].

6.1 Clinical Trial Experience

A total of 844 patients on teriflunomide (7 mg or 14 mg once daily) constituted the safety population in the pooled analysis of placebo controlled studies in patients with relapsing forms of MS (RMS). Approximately 72% of patients were female and the mean age was 38 years.

Study 1 was a 108-week placebo-controlled clinical study in 1086 RMS patients treated with teriflunomide 7 mg (n=368), teriflunomide 14 mg (n=358), or placebo (n=360).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Table 1 Adverse Reactions in Study 1 (occurring in $\geq 2\%$ of patients, and reported for teriflunomide 7 mg or 14 mg at $\geq 2\%$ higher rate than for placebo)

Teriflunomide

PRIMARY SYSTEM ORGAN CLASS Preferred Term (%)	14 mg (N=358)	7 mg (N=368)	Placebo (N=360)
INFECTIONS AND INFESTATIONS			
Influenza	12%	9%	10%
Upper respiratory tract infection	9%	9%	7%
Bronchitis	8%	5%	6%
Sinusitis	6%	4%	4%
Cystitis	4%	2%	1%
Gastroenteritis viral	4%	2%	1%
Oral herpes	4%	2%	2%
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Neutropenia	4%	2%	0.3%
Leukopenia	1%	2%	0.3%
IMMUNE SYSTEM DISORDERS			
Seasonal allergy	3%	2%	1%
PSYCHIATRIC DISORDERS			
Anxiety	4%	3%	2%
NERVOUS SYSTEM DISORDERS			
Headache	19%	22%	18%
Paraesthesia	10%	9%	8%
Sciatica	3%	1%	1%
Burning sensation	3%	2%	1%
Carpal tunnel syndrome	3%	1%	0.3%
EYE DISORDERS			
Vision blurred	3%	3%	1%
Conjunctivitis	1%	3%	1%
CARDIAC DISORDERS			
Palpitations	2%	3%	1%
VASCULAR DISORDERS			
Hypertension	4%	4%	2%
GASTROINTESTINAL DISORDERS			
Diarrhoea	18%	15%	9%
Nausea	14%	9%	7%
Abdominal pain upper	6%	5%	4%
Toothache	4%	4%	2%
Abdominal distension	1%	2%	0.3%

PRIMARY SYSTEM ORGAN CLASS Preferred Term (%)	Teriflunomide		Placebo (N=360)
	14 mg (N=358)	7 mg (N=368)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia	13%	10%	3%
Acne	3%	1%	1%
Pruritus	3%	4%	2%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Musculoskeletal pain	4%	5%	3%
Myalgia	3%	4%	2%
INVESTIGATIONS			
Alanine aminotransferase increased	14%	12%	7%
Gamma-glutamyltransferase increased	3%	5%	1%
Aspartate aminotransferase increased	3%	2%	1%
Weight decreased	2%	3%	1%
Neutrophil count decreased	2%	3%	0.3%
White blood cell count decreased	1%	3%	0%

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, 18% of teriflunomide-treated subjects had mild hypophosphatemia (≥ 0.6 mmol/L and $<$ lower limit of normal), compared to 9% of placebo-treated subjects; 5% of teriflunomide-treated subjects had moderate hypophosphatemia (≥ 0.3 mmol/L and < 0.6 mmol/L), compared to 1% of placebo-treated subjects. No subject in either treatment group had a serum phosphorus < 0.3 mmol/L.

7. DRUG INTERACTIONS

Effect of teriflunomide on CYP2C8 substrates

There was an increase in mean repaglinide C_{\max} and AUC (1.7- and 2.4-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.

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 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. 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 C_{\max} and AUC of caffeine (CYP1A2 substrate) by 18% and 55% respectively, suggesting that teriflunomide may be *in vivo* a weak inducer of CYP1A2. Therefore, patients should be monitored when teriflunomide is coadministered with drugs metabolized by CYP1A2 (such as duloxetine, alosetron, theophylline, and tizanidine), as the efficacy of such drugs could be reduced.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4.2) and Warnings and Precautions (5.2)]

When teriflunomide (oral doses of 1, 3, or 10 mg/kg/day) was administered to pregnant rats throughout the period of organogenesis, high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death were observed at doses not associated with maternal toxicity. Adverse effects on embryofetal development were observed following dosing at various stages throughout organogenesis. Maternal plasma exposure at the no-effect level (1.0 mg/kg/day) for embryofetal developmental toxicity in rats was less than that in humans at the maximum recommended human dose (MRHD, 14 mg/day).

Administration of teriflunomide (oral doses of 1, 3.5, or 12 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with minimal maternal toxicity. Maternal plasma exposure at the no-effect dose (1.0 mg/kg/day) for embryofetal developmental toxicity in rabbits was less than that in humans at the MRHD.

In studies in which teriflunomide (oral doses of 0.05, 0.1, 0.3, 0.6, or 1.0 mg/kg/day) was administered to rats during gestation and lactation, decreased growth, eye and skin abnormalities, and high incidences of malformation (limb defects) and postnatal death were observed in the offspring at doses not associated with maternal toxicity. Maternal plasma exposure at the no-effect dose for pre- and postnatal developmental toxicity in rats (0.10 mg/kg/day) was less than that in humans at the MRHD.

In animal reproduction studies of leflunomide, embryoletality and teratogenic effects were observed in pregnant rat and rabbit at or below clinically relevant plasma teriflunomide exposures (AUC). In published reproduction studies in pregnant mice, leflunomide was embryoletal and increased the incidence of malformations (craniofacial, axial skeletal, heart and great vessel). Supplementation with exogenous uridine reduced the teratogenic effects in pregnant mice, suggesting that the mode of action (inhibition of mitochondrial enzyme dihydroorotate dehydrogenase) is the same for therapeutic efficacy and developmental toxicity. At recommended doses in humans, teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide.

Use in Males

AUBAGIO 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 (0.02 µg/mL). [see *Warnings and Precautions* (5.3)]

Pregnancy Registry

Although AUBAGIO is contraindicated in pregnancy, a pregnancy registry has been established to monitor fetal outcomes of pregnant women exposed to AUBAGIO. Physicians are encouraged to enroll pregnant women in the AUBAGIO pregnancy registry, or pregnant women may enroll themselves, by calling 1-800-745-4447, option 2.

8.3 Nursing Mothers

Teriflunomide was detected in rat milk following a single oral dose of teriflunomide. 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of AUBAGIO did not include patients over 65 years old.

8.6 Hepatic Impairment

No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. The pharmacokinetics of teriflunomide in severe hepatic impairment have not been evaluated.

Teriflunomide is contraindicated in patients with severe hepatic impairment [see *Contraindications (4.1) and Warnings and Precautions (5.3)*].

8.7 Renal Impairment

No dosage adjustment is necessary for patients with mild, moderate, and severe renal impairment [see *Clinical Pharmacology (12.3)*].

10. OVERDOSAGE

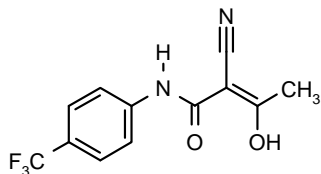
There is no experience regarding teriflunomide overdose or intoxication in humans.

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

In the event of clinically significant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination [see *Warnings and Precautions (5.3)*].

11. DESCRIPTION

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 $C_{12}H_9F_3N_2O_2$ 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.

Teriflunomide is formulated as film-coated tablets for oral administration. AUBAGIO tablets contain 7 mg or 14 mg of teriflunomide and the following inactive 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. In addition to these, the 7 mg tablet film coating includes iron oxide yellow.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Teriflunomide, an immunomodulatory agent with anti-inflammatory properties, inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. The exact mechanism by which teriflunomide exerts its therapeutic effect in multiple

sclerosis is unknown but may involve a reduction in the number of activated lymphocytes in CNS.

12.2 Pharmacodynamics

Potential to prolong the QT interval

In a placebo controlled thorough QT study performed in healthy subjects, there was no evidence that teriflunomide caused QT interval prolongation of clinical significance (i.e., the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 ms).

12.3 Pharmacokinetics

Teriflunomide is the principal 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 analysis of teriflunomide in healthy volunteers and MS patients, median t_{1/2} 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 or 14 mg.

Absorption

Median time to reach maximum plasma concentrations is 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 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 eliminated mainly through direct biliary excretion of unchanged drug as well as renal excretion of metabolites. Over 21 days, 60.1% of the administered dose is excreted via feces (37.5%) and urine (22.6%). After an 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.

Drug Interactions:

Teriflunomide is not metabolized by Cytochrome P450 or flavin monoamine oxidase enzymes. Based on *in vitro* studies, teriflunomide is a substrate of the efflux transporter Breast Cancer

Resistant Protein (BCRP). BCRP inhibitors (such as cyclosporine, eltrombopag, gefitinib) may increase exposure of teriflunomide.

In vitro and *in vivo* studies suggested teriflunomide is an inhibitor of CYP2C8 and an *in vivo* study with caffeine indicated that teriflunomide induces CYP1A2. Teriflunomide is also an inhibitor of BCRP, hepatic uptake transporter (OATP1B1), and renal uptake transporter (OAT3). *In vivo* studies to confirm transporter based interaction have not been conducted.

Potential of Other Drugs to Affect AUBAGIO:

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

Potential of AUBAGIO to Affect Other Drugs:

Teriflunomide did not affect the pharmacokinetics of bupropion (a CYP2B6 substrate), midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), omeprazole (a CYP2C19 substrate) and metoprolol (a CYP2D6 substrate).

Special populations

Hepatic Impairment: Mild and moderate hepatic impairment had no impact on the pharmacokinetics of teriflunomide. The pharmacokinetics of teriflunomide in severe hepatic impairment have not been evaluated [see *Contraindications (4.1)*].

Renal Impairment: Severe renal impairment had no impact on the pharmacokinetics of teriflunomide [see *Use in Specific Populations (8.7)*].

Gender: In a population analysis, there was a 23% decrease in clearance in females compared to males.

Race: Effect of race on the pharmacokinetics of teriflunomide cannot be adequately assessed due to a low number of non-white patients in the clinical trials.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: No evidence of carcinogenicity was observed in lifetime carcinogenicity bioassays in mouse and rat. In mouse, teriflunomide was administered orally at doses up to 12 mg/kg/day for up to 95-104 weeks; plasma teriflunomide exposures (AUC) at the highest dose tested are approximately 3 times that in humans at the maximum recommended human dose (MRHD, 14 mg/day). In rat, teriflunomide was administered orally at doses up to 4 mg/kg/day for up to 97-104 weeks; plasma teriflunomide AUCs at the highest doses tested are less than that in humans at the MRHD.

Mutagenesis: Teriflunomide was negative in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vitro* HPRT assay, and in *in vivo* micronucleus and chromosomal aberration assays. 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 positive in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vitro* HPRT assay, and the *in vitro* chromosomal aberration assay in mammalian cells. 4-TFMA was negative in *in vivo* micronucleus and chromosomal aberration assays.

Impairment of fertility: Oral administration of teriflunomide (0, 1, 3, 10 mg/kg/day) to male rats prior to and during mating (to untreated females) resulted in no adverse effects on fertility; however, reduced epididymal sperm count was observed at the mid and high doses tested. The no-effect dose for reproductive toxicity in male rats (1 mg/kg) is less than the MRHD on a mg/m² basis.

Oral administration of teriflunomide (0, 0.84, 2.6, 8.6 mg/kg/day) to female rats, prior to and during mating (to untreated males) and continuing to gestation day 6, resulted in embryoletality, reduced fetal body weight, and/or malformations at all doses tested. Due to marked embryoletality at the highest dose tested, no fetuses were available for evaluation. The lowest dose tested is less than the MRHD on a mg/m² basis.

14. CLINICAL STUDIES

The efficacy of AUBAGIO was demonstrated in Study 1, 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 7mg 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 (see 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 time to 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 (see 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 (See Table 2).

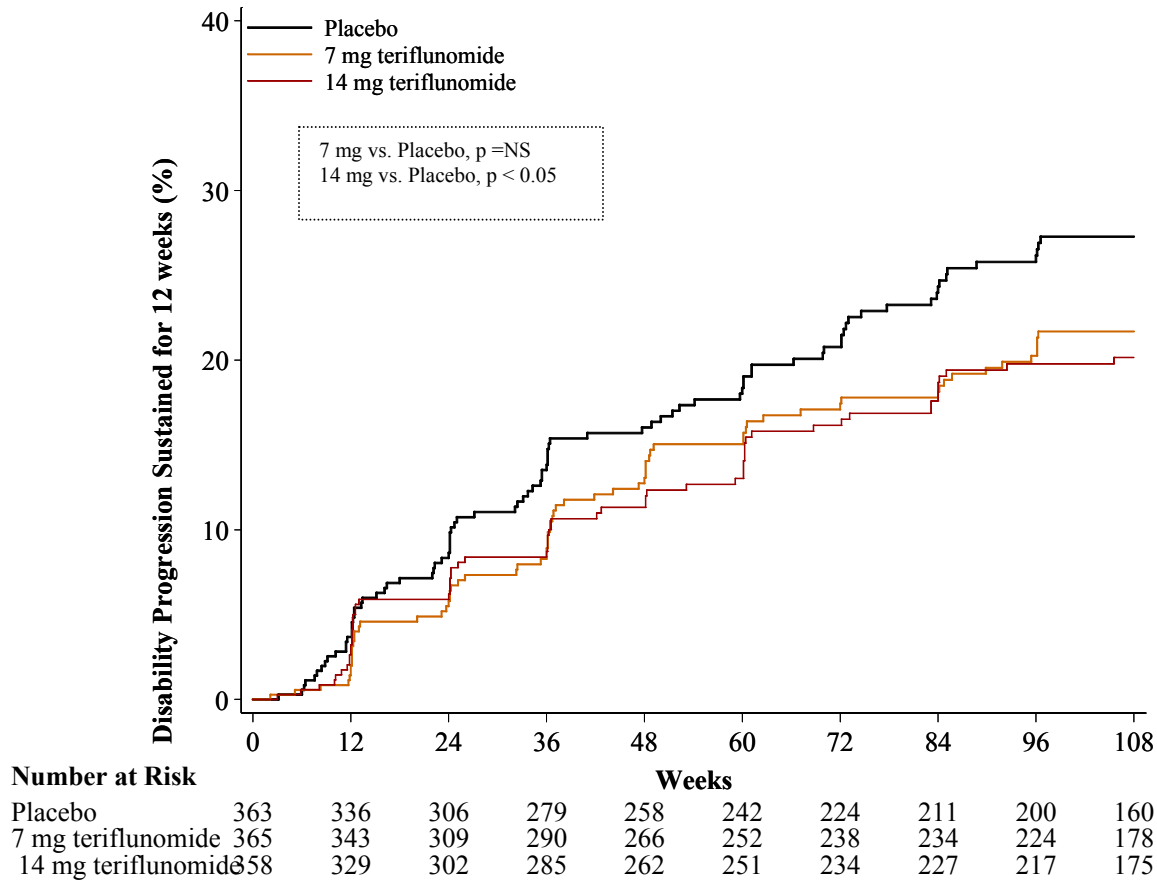
Table 2 Clinical and MRI Results of Study 1

	TN 14 mg N=358	TN 7 mg N=365	Placebo N=363
Clinical Endpoints			
Annualized relapse rate (primary endpoint)	0.369 (p = 0.0005)	0.370 (p = 0.0002)	0.539
Relative risk reduction	31%	31%	
Percent of patients remaining relapse-free at week 108	56.5%	53.7%	45.6%
Percent disability progression at week 108	20.2% (p = 0.028)	21.7% (p = 0.084)	27.3%
Hazard ratio	0.70	0.76	
MRI Endpoints			
Median change from baseline in Total lesion volume ¹ (mL) at week 108	0.345 (p = 0.0003) ²	0.755 (p= 0.0317) ²	1.127
Mean number of Gd-enhancing T1-lesions per scan	0.261 (p < 0.0001)	0.570 (p < 0.0001)	1.331

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 - ITT population



The effect of teriflunomide on MRI activity was also demonstrated in Study 2, 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).

16. HOW SUPPLIED/STORAGE AND HANDLING

AUBAGIO is available 7 mg and 14 mg tablets.

The 14 mg tablet is 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.

The 7 mg tablet is very light greenish-bluish grey to pale greenish-blue, hexagonal film-coated tablets with dose strength “7” imprinted on one side and engraved with corporate logo on other side. Each tablet contains 7 mg of teriflunomide.

AUBAGIO 14 mg tablets are supplied as:

NDC 58468-0210-2 Carton of 28 tablets containing 1 wallet composed of 2 folded blister cards of 14 tablets per blister card

NDC 58468-0210-1 Carton of 5 tablets with one blister card with five tablets

AUBAGIO 7 mg tablets are supplied as:

NDC 58468-0211-1 Carton of 28 tablets containing 1 wallet composed of 2 folded blister cards of 14 tablets per blister card

NDC 58468-0211-2 Carton of 5 tablets with one blister card with five tablets

Store at 68°F to 77°F (20°C to 25°C) with excursions permitted between 59°F and 86°F (15°C and 30°C).

17. PATIENT COUNSELING INFORMATION

See Medication Guide.

A Medication Guide is required for distribution with AUBAGIO. Encourage patients to read the AUBAGIO Medication Guide. The complete text of the Medication Guide is reprinted at the end of this document.

17.1 Benefits and Risks

Summarize for patients the benefits and potential risks of treatment with AUBAGIO. Tell patients to take AUBAGIO once daily as prescribed. Tell patients not to discontinue AUBAGIO without first discussing with the prescribing physician.

17.2 Hepatotoxicity

Inform patients that AUBAGIO may increase liver enzymes and that their liver enzymes will be checked before starting AUBAGIO and for at least 6 months while they are taking AUBAGIO. Advise patients that they should contact their physician if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine.

17.3 Importance of Preventing Pregnancy

- Inform patients that based on animal studies, AUBAGIO may cause fetal harm.
- Advise women of childbearing potential of the need for effective contraception during AUBAGIO treatment and until completion of an accelerated elimination procedure. Advise them that an accelerated elimination procedure can be used at any time after the discontinuation of AUBAGIO.

- Instruct the patient that if she suspects or confirms pregnancy, she should immediately inform her physician. Inform the patients that an AUBAGIO pregnancy registry is available.
- Instruct men who are taking AUBAGIO and wish to father a child to discontinue AUBAGIO and use an accelerated elimination procedure. Instruct men taking AUBAGIO who do not wish to father a child that they and their female partners should use reliable contraception.

17.4 Availability of an Accelerated Elimination Procedure

Advise patients that AUBAGIO may stay in the blood for up to 2 years after the last dose and that an accelerated elimination procedure may be used if needed.

17.5 Risk of Infections

Inform patients that they may develop a lowering of their white blood cell counts and that their blood counts will be checked before starting AUBAGIO.

Inform patients that they may be more likely to get infections when taking AUBAGIO and that they should contact their physician if they develop symptoms of infection, particularly in case of fever.

Advise patients that the use of some vaccines should be avoided during treatment with AUBAGIO and for at least 6 months after discontinuation.

17.6 Peripheral Neuropathy

Inform patients that they may develop peripheral neuropathy. Advise patients that they should contact their physician if they develop symptoms of peripheral neuropathy, such as numbness or tingling of hands or feet.

17.7 Blood Pressure Effects

Inform patients that AUBAGIO may increase blood pressure.

17.8 Nursing mothers

Inform patients that it is not known whether this drug is present in human milk. Advise patients to discontinue breastfeeding or discontinue the drug.

Medication Guide

AUBAGIO (*oh-BAH-gee-oh*) (teriflunomide) tablets

Read this Medication Guide before you start using AUBAGIO and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about AUBAGIO?

AUBAGIO may cause serious side effects, including:

- **Liver problems:** AUBAGIO may cause serious liver problems that may lead to death. Your risk of liver problems may be higher if you take other medicines that also affect your liver. Your doctor should do blood tests to check your liver:
 - within 6 months before you start taking AUBAGIO
 - 1 time a month for 6 months after you start taking AUBAGIO

Call your doctor right away if you have any of the following symptoms of liver problems:

- nausea
 - vomiting
 - stomach pain
 - loss of appetite
 - tiredness
 - your skin or the whites of your eyes turn yellow
 - dark urine
- **Harm to your unborn baby:** AUBAGIO may cause harm to your unborn baby. Do not take AUBAGIO if you are pregnant. Do not take AUBAGIO unless you are using effective birth control.
 - If you are a female, you should have a pregnancy test before you start taking AUBAGIO. Use effective birth control during your treatment with AUBAGIO.
 - After stopping AUBAGIO, continue using effective birth control until you have blood tests to make sure your blood levels of AUBAGIO are low enough. If you become pregnant while taking AUBAGIO or within 2 years after you stop taking it, tell your doctor right away.
 - **AUBAGIO Pregnancy Registry.** If you become pregnant while taking AUBAGIO or during the 2 years 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 your health and your baby's health.
 - **For men taking AUBAGIO:**

- If your female partner plans to become pregnant, you should stop taking AUBAGIO and ask your doctor how to quickly lower the levels of AUBAGIO in your blood.
- If your female partner does not plan to become pregnant, you and your female partner should use effective birth control during your treatment with AUBAGIO. AUBAGIO remains in your blood after you stop taking it, so continue using effective birth control until AUBAGIO blood levels have been checked and they are low enough.

AUBAGIO may stay in your blood for up to 2 years after you stop taking it. Your doctor can prescribe a medicine to help lower your blood levels of AUBAGIO more quickly. Talk to your doctor if you want more information about this.

What is AUBAGIO?

AUBAGIO is a prescription medicine used to treat relapsing forms of multiple sclerosis (MS). AUBAGIO can decrease the number of MS flare-ups (relapses). AUBAGIO does not cure MS, but it can help slow down the physical problems that MS causes.

It is not known if AUBAGIO is safe and effective in children.

Who should not take AUBAGIO?

Do not take AUBAGIO if you:

- have severe liver problems
- are pregnant or are of childbearing age and not using effective birth control
- take a medicine called leflunomide

What should I tell my doctor before taking AUBAGIO?

Before you take AUBAGIO, tell your doctor if you:

- have liver or kidney problems
- have a fever or infection, or you are unable to fight infections
- have numbness or tingling in your hands or feet that is different from your MS symptoms
- have diabetes
- have had serious skin problems when taking other medicines
- have breathing problems
- have high blood pressure
- 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.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using AUBAGIO and other medicines may affect each other causing serious side effects. AUBAGIO may affect the way other medicines work, and other medicines may affect how AUBAGIO works.

Especially tell your doctor if you take medicines that could raise your chance of getting infections, including medicines used 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.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take AUBAGIO?

- Take AUBAGIO exactly as your doctor tells you to take it.
- Take AUBAGIO 1 time each day.
- Take AUBAGIO with or without food.

What are possible side effects of AUBAGIO?

AUBAGIO may cause serious side effects, including:

- See **“What is the most important information I should know about AUBAGIO?”**
- **decreases in your white blood cell count.** Your white blood cell counts should be checked before you start taking AUBAGIO. When you have a low white blood cell count you:
 - **may have more frequent infections.** You should have a skin test for TB (Tuberculosis) before you start taking AUBAGIO. Tell your doctor if you have any of these symptoms of an infection:
 - fever
 - tiredness
 - body aches
 - chills
 - nausea
 - vomiting

- **should not receive certain vaccinations during your treatment** with AUBAGIO and for 6 months after your treatment with AUBAGIO ends.
- **numbness or tingling in your hands or feet that is different from your MS symptoms.** You have a greater chance of getting peripheral neuropathy if you:
 - are over 60 years of age
 - take certain medicines that affect your nervous system
 - have diabetes

Tell your doctor if you have numbness or tingling in your hands or feet that is different from your MS.

- **kidney problems** . Tell your doctor if you have pain in your side (flank pain).
- **high potassium levels in your blood.** Tell your doctor if you have nausea that does not go away or a racing heartbeat.
- **serious skin problems.** Tell your doctor if you have any skin problems such as redness and peeling.
- **new or worsening breathing problems.** Tell your doctor if you have shortness of breath or coughing with or without fever.
- **high blood pressure.** Your doctor should check your blood pressure before you start taking AUBAGIO and while you are taking AUBAGIO.

The most common side effects of AUBAGIO include:

- increases in the results of blood tests to check your liver
- hair thinning or loss (alopecia)
- diarrhea
- flu
- nausea
- burning or prickling feeling in your skin (paraesthesia)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of AUBAGIO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-332-1088.

How should I store AUBAGIO?

- Store AUBAGIO at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep AUBAGIO and all medicines out of reach of children.

General information about the safe and effective use of AUBAGIO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AUBAGIO for a condition for which it was not prescribed. Do not give AUBAGIO to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about AUBAGIO. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about AUBAGIO that is written for healthcare professionals.

For more information, go to www.aubagio.com or call Genzyme Medical Information Services at 1-800-745-4447, option 2.

What are the ingredients in AUBAGIO?

Active ingredient: teriflunomide

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
A Sanofi Company

September 2012

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
09/12/2012