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

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 < $1.5x10^9$/L was observed in 10% and 15% of patients on AUBAGIO 7

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