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 use
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 lefluno-
  mide 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
  Teratogenicity and embryolethality occurred in animals administered teriflunomide (5.2, 5.3, 8.1). If patient develops symptoms consistent with peripheral neuropathy, evaluate patient and consider discontinuing AUBAGIO (5.6).

CONTRAINDICATIONS
- Severe hepatic impairment (4, 5.1)
- Pregnancy (4, 5.2, 8.1)
- Hypersensitivity (4, 5.5)
- Current leflunomide treatment (4)

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 in case of serious infection. Do not start AUBAGIO in patients with active infections (5.4).
- Stop AUBAGIO if patient has anaphylaxis, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis; initiate rapid elimination (5.3, 5.5).

ADVERSE REACTIONS
Most common adverse reactions (≥10% and ≥2% greater than placebo): headache, diarrhea, nausea, alopecia, increase in ALT (6).

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

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

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2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
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Revised: 11/2016

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)
- Pregnancy (4, 5.2, 8.1)
- Hypersensitivity (4, 5.5)
- Current leflunomide treatment (4)

Warnings and Precautions, Respiratory Effects (5.8)

Drug Interactions
- Drugs metabolized by CYP2C8 and OAT3 transporters: Monitor patients because teriflunomide may increase exposure of these drugs (7).
- Teriflunomide may increase exposure of ethinylestradiol and levonorgestrel. Choose an appropriate oral contraceptive (7).
- Drugs metabolized by CYP1A2: Monitor patients because teriflunomide may decrease exposure of these drugs (7).
- Drugs metabolized by BCRP and OATP1B1/B3 transporters: Monitor patients because teriflunomide may increase exposure of these drugs (7).
- Rosuvastatin: The dose of rosuvastatin should not exceed 10 mg once daily in patients taking AUBAGIO (7).

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

AUBAGIO is contraindicated in patients with severe hepatic impairment [see Contraindications (4)]. Patients with pre-existing liver disease may be at an increased risk of developing elevated serum transaminases when taking AUBAGIO.

Risk of Teratogenicity
AUBAGIO is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Teratogenicity and embryolethality occurred in animals at plasma teriflunomide exposures similar to or lower than that in humans at the maximum human recommended dose (MHRD) of 14 mg/day [see Use in Specific Populations (8.1)]. AUBAGIO is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception [see Contraindications (4) and Warnings and Precautions (5.3)].

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

4 CONTRAINDICATIONS

AUBAGIO is contraindicated in:

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

• Pregnant women and females of reproductive potential not using effective contraception [see Contraindications (4) and Use in Specific Populations (8.1)].

• Patients with a history of a hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in AUBAGIO. Reactions have included anaphylaxis, angioedema, and serious skin reactions [see Warnings and Precautions (5.5)].

• Co-administration with leflunomide [see Clinical Pharmacology (12.3)].

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. 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)]. Patients with pre-existing liver disease may be at an increased risk of developing elevated serum transaminases when taking AUBAGIO.

5.2 Teratogenicity

AUBAGIO may cause fetal harm when administered to a pregnant woman. Teratogenicity and embryolethality occurred in animals at plasma teriflunomide exposures similar to or lower than that in humans at the maximum human recommended dose (MHRD) of 14 mg/day [see Use in Specific Populations (8.1)]. AUBAGIO is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception [see Contraindications (4) and Warnings and Precautions (5.3)].

5.3 Procedure for Accelerated Elimination of Teriflunomide

Teriflunomide is eliminated slowly from the plasma [see Clinical Pharmacology (12.3)]. 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 differences in the rate of elimination, some patients 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

Bone Marrow Effects

A mean decrease compared to baseline 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 2 weeks, at which time WBC counts were 25% lower than baseline and remained low during placebo-controlled studies. Neutrophil count <1.5×10^9/L was observed in 12% and 16% of patients receiving AUBAGIO 7 mg and 14 mg, respectively, compared with 7% of patients receiving placebo; lymphocyte count <0.8×10^9/L was observed in 10% and 12% of patients receiving AUBAGIO 7 mg and 14 mg, respectively, compared with 6% of patients receiving placebo. Cases of pancytopenia with or without platelet count <50,000/mm^3, have been reported in the postmarketing setting. 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

AUBAGIO may cause neutropenia and may predispose patients to infection. In clinical studies with AUBAGIO, cyto-

phagocytic ulcerations have been reported in the postmarketing setting. Medications like AUBAGIO that have the potential to 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 AUBAGIO 7 mg (2.2%) or 14 mg (2.7%) compared to placebo (2.2%). However, one fatal case of klebsiella pneumonia sepsis occurred in a patient taking AUBAGIO 14 mg for 1.7 years. Fatal infections have been reported in the postmarketing 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 therapeutic use, 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 or with a blood test for mycobacterium tuberculosis infection [see Warnings and Precautions (5.4)].

Patients with a history of tuberculosis, the presence of tuberculous lesions, or with history of high-risk exposure should be confirmed by standard medical practice prior to resuming treatment with AUBAGIO.

In placebo-controlled studies, ALT greater than three times the ULN occurred in 61/1045 (5.8%) and 62/1002 (6.2%) of patients receiving AUBAGIO 7 mg and 14 mg, respectively, and 38/997 (3.8%) of patients receiving 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 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. AUBAGIO-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 after starting AUBAGIO. Consider additional monitoring when AUBAGIO is given with other potentially hepatotoxic drugs.

Consider discontinue AUBAGIO if serum transaminase increase (greater than three times the ULN) is confirmed. Monitor serum transaminase and bilirubin on AUBAGIO therapy, particularly in patients with abnormal liver function tests. 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 AUBAGIO and start an accelerated elimination procedure [see Warnings and Precautions (5.3)] and monitor liver tests weekly until normalized. If AUBAGIO-induced liver injury is unlikely because some other probable cause has been found, resumption of AUBAGIO therapy may be considered.
Cases of serious skin reactions, including cases of Stevens-Johnson syndrome (SJS) and a fatal case of toxic epidermal necrolysis (TEN), have been reported with AUBAGIO. In patients treated with iflunomide, the parent compound, very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported.

Informed patients of the signs and symptoms of anaphylaxis and angioedema and signs and symptoms that may signal liver, cardiovascular, or hematologic reactions associated with signs of other organ system involvement (e.g., rash, lymphadenopathy, or hepatic dysfunction) may be drug-related. Instruct patients to discontinue AUBAGIO and seek immediate medical care should these signs and symptoms occur. Discontinue AUBAGIO, unless the reactions are clearly not drug-related, and begin an accelerated elimination procedure immediately [see Warnings and Precautions (5.3)]. In such cases, patients should not be re-exposed to teriflunomide [see Contraindications (4)].

### 5.5 Peripheral Neuropathy

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), occurred more frequently in patients taking AUBAGIO than in patients taking placebo. The incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.4% (13 patients) and 1.9% (17 patients) of patients receiving 7 mg and 14 mg of AUBAGIO, respectively, compared with 0.4% receiving placebo (4 patients). Treatment was discontinued in 0.7% (8 patients) with confirmed peripheral neuropathy (3 patients receiving AUBAGIO 7 mg and 5 patients receiving AUBAGIO 14 mg). Five of them recovered following treatment discontinuation. Not all cases of peripheral neuropathy resolved with continued treatment. Peripheral neuropathy also occurred in patients receiving iflunomide.

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 Peripheral Neuropathy

### 5.7 Increased Blood Pressure

In placebo-controlled studies, the mean change from baseline to the end of study in systolic blood pressure was +2.3 mmHg and +2.7 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -0.6 mmHg for placebo. The change from baseline in diastolic blood pressure was +1.4 mmHg and +1.3 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -0.8 mmHg for placebo. Hypertension was an adverse reaction in 3.1% and 4.3% of patients treated with 7 mg and 14 mg of AUBAGIO compared with 1.8% for placebo. The change from baseline in diastolic blood pressure was +2.3 mmHg and +2.7 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -0.6 mmHg for placebo. Check blood pressure before start of AUBAGIO treatment and periodically thereafter. Elevated blood pressure should be appropriately managed during treatment with AUBAGIO.

### 5.8 Respiratory Effects

Interstitial lung disease, including acute interstitial pneumonitis, has been reported with AUBAGIO in the postmarketing setting. Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during treatment with AUBAGIO and iflunomide. Interstitial lung disease may be fatal and may occur acutely at any time during a therapy with 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 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)].

### 5.9 Concomitant Use with Immunosuppressive or Immunomodulating Therapies

Coadministration with antineoplastic, or immunosuppressive therapies used for treatment of multiple sclerosis has not been evaluated. Safety studies in which AUBAGIO 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:

- Hypersensitivity [see Contraindications (4) and Warnings and Precautions (5.1)]
- Bone Marrow Effects/Immunosuppression Potential/Infections [see Warnings and Precautions (5.4)]
- Hypersensitivity and Serious Skin Reactions [see Contraindications (4) and Warnings and Precautions (5.5)]
- Peripheral Neuropathy [see Warnings and Precautions (5.6)]
- Increased Blood Pressure [see Warnings and Precautions (5.7)]
- Respiratory Effects [see Warnings and Precautions (5.8)]

#### 6.1 Clinical Trials Experience

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 clinical or commercial experience or to the adverse reaction rates reported for a drug used in clinical practice. A total of 2047 patients receiving AUBAGIO (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 multiple sclerosis; of these, 71% were female. The average age was 37 years. Table 1 lists adverse reactions in placebo-controlled trials for rates that were at least 2% for AUBAGIO patients and also at least 2% above the rate in placebo patients. The most common were headache, an increase in ALT, diabetes, alopecia, and nausea. The adverse reaction most commonly associated with discontinuation was an increase in ALT (3.3%, 2.6%, and 2.3% of all patients in the AUBAGIO 7 mg, AUBAGIO 14 mg, and placebo treatment arms, respectively). 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)].

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AUBAGIO 7 mg (N=1045)</th>
<th>AUBAGIO 14 mg (N=1002)</th>
<th>Placebo (N=997)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18%</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13%</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>10%</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
</tr>
</tbody>
</table>

### 7 DRUG INTERACTIONS

**Effect of AUBAGIO on CYP2C8 substrates**

Teriflunomide is an inhibitor of CYP2C8 in vivo. In patients taking AUBAGIO, exposure of drugs metabolized by CYP2C8 (e.g., paxilactine, pioglitazone, repaglinide, sitagliptin) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP2C8 as required [see Clinical Pharmacology (12.3)].

**Effect of AUBAGIO on warfarin**

Co-administration of AUBAGIO with warfarin requires close monitoring of the international normalized ratio (INR) because AUBAGIO may decrease peak INR by approximately 25%. Use of AUBAGIO on oral anticoagulants may increase the systemic exposures of ethinylestradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with AUBAGIO [see Clinical Pharmacology (12.3)].

**Effect of AUBAGIO on CYP1A2 substrates**

Teriflunomide may be a weak inducer of CYP1A2 in vivo. In patients taking AUBAGIO, exposure of drugs metabolized by CYP1A2 (e.g., alosetron, duloxetine, theophylline, tizanidine) may be reduced. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP1A2 as required [see Clinical Pharmacology (12.3)].

**Effect of AUBAGIO on organic anion transporter 3 (OAT3) substrates**

Teriflunomide inhibits the activity of OAT3 in vitro. In patients taking AUBAGIO, exposure of drugs which are OAT3 substrates (e.g., ecfagist, cimetidine, ciprofloxacin, penicillin G, keprofen, tiosarmide, mexitelate, zidovudine) may be increased. Monitor these patients and adjust the dose of the coadministered drug(s) which are OAT3 substrates as required [see Clinical Pharmacology (12.3)].

**Effect of AUBAGIO on BCRP and organic anion transporting polypeptide B1 and B3 (OATP1B1/1B3) substrates**

Teriflunomide inhibits the activity of BCRP and OATP1B1/1B3 in vivo. For a patient taking AUBAGIO, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., mitoxantrone) and drugs in the OATP family (e.g., metrotrexate, rifampin), especially HMG-CoA reductase inhibitors (e.g., atorvastatin, raltegravir, pravastatin, repaglinide, and simvastatin), consider reducing the dose of these drugs and monitor patients closely for signs and symptoms of increased exposure to the drugs used to treat AUBAGIO [see Clinical Pharmacology (12.3)].

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Pregnancy Exposure Registry**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AUBAGIO during pregnancy. Health care providers and patients are encouraged to report pregnancies by calling 1-800-745-4447, option 2.

**Risk Summary**

AUBAGIO is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception because of the potential for fetal harm based on animal data. Human data are not available at this time to inform the presence or absence of drug-associated risk with the use of AUBAGIO during pregnancy.

In animal reproduction studies in rat and rabbits, oral administration of teriflunomide during organogenesis caused reduced body weight gain and reduced body weight at weaning in the offspring and increased fetal resorptions, stillbirths, and fetuses with external and internal abnormalities (AUC) lower than that of the maximum recommended dose (MRHD) of 14 mg/day (see Data). In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage in the indicated population is unknown.

**Clinical Considerations**

Women who wish to become pregnant 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 mcg/mL). Effective contraception should be used until it is verified that plasma
Teriflunomide is a white to almost white powder that is sparingly soluble in acetone, slightly soluble in ethanol and water (22.6%). After an accelerated elimination procedure with cholestyramine, an additional 23.1% of the administered dose is excreted in the feces (37.5%) and urine (22.6%). 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% of the administered dose is excreted in the feces (37.5%) and urine (22.6%).

**Elimination**

Teriflunomide is the major circulating moiety detected in plasma. The primary biliary excretory process involves a reduction in the number of activated lymphocytes in CNS. 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.

**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 t1/2 was approximately 18 and 19 days after repeated doses of 7 mg and 14 mg respectively. It takes approximately 3 months and 4 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 (>98%) 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 biliary transformation pathway to minor metabolites of teriflunomide is hydroxylation, 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 3.05 mL/h.

**Drug Interaction Studies**

Teriflunomide is not metabolized by Cytochrome P450 or flavin monooxidase enzymes.

The Potential Effect of AUBAGIO on Other Drugs

- **CYP2C8 Substrates**
  - There was an increase in mean regapentin Cmax and AUC (1.58- and 1.54-fold, respectively) following repeated doses of teriflunomide and a single dose of 0.25 mg regapentin, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo. The magnitude of interaction could be higher at the recommended regapentin dose [see Drug Interactions (7)].

- **CYP1A2 Substrates**
  - Reduced doses of teriflunomide decreased mean Cmax and AUC of caffeine by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 in vivo [see Drug Interactions (7)].

- **OAT3 Substrates**
  - There was an increase in mean cefaclor Cmax and AUC (1.43- and 1.54-fold, respectively) following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of BCRP transporter and organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1/1B3) [see Drug Interactions (7)].

- **BCRP and OATP1B1/1B3 Substrates**
  - There was an increase in mean rosuvastatin Cmax and AUC (2.65- and 2.51-fold, respectively) following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of BCRP transporter and organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1/1B3) [see Drug Interactions (7)].

- **Oral Contraceptives**
  - There was an increase in mean ethinylestradiol Cmax and AUCO-24 (1.58- and 1.54-fold, respectively) and levonorgestrel Cmax and AUCO-24 (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide [see Drug Interactions (7)].

- **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).**

- **Potential effect on Other Drugs on AUBAGIO**
  - CYP and transporter inducers: Rifampin did not affect the pharmacokinetics of teriflunomide.
Specific populations

- Hepatic impairment
- Renal impairment
- Severe renal impairment
- Gender
- Race

In a population analysis, the clearance rate for teriflunomide is 23% less in females than in males.

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 mice 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 in vitro bacterial reverse mutation (Ames) assay, in the in vitro HPR assay, and 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 the in vitro urine 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.

In a fertility study, 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, 0.94, 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 embryolethality, reduced fetal body weight, and/or malformations at all doses tested. Due to marked embryolethality 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

Four randomized, controlled, double-blind clinical trials established the efficacy of AUBAGIO in patients with relapsing forms of multiple sclerosis.

Study 1 was a double-blind, placebo-controlled clinical trial that evaluated once daily doses of AUBAGIO 7 mg and AUBAGIO 14 mg for up to 26 months in patients with relapsing forms of multiple sclerosis. Patients were required to have a diagnosis of multiple sclerosis exhibiting a relapsing clinical course, and to have experienced at least one relapse over the year preceding the trial or at least two relapses over the two years preceding the trial. Patients were required not to have received interferon-beta for at least four months, or any other multiple sclerosis medication until completion, and after every suspected relapse. The primary end point was the ARR.

A total of 1165 patients received AUBAGIO 7 mg (n=407), AUBAGIO 14 mg (n=370), or placebo (n=388). Patients had a mean age of 38 years, a mean disease duration of 5 years, and a mean EDSS at baseline ≤ 5.5. Patients had a mean age of 38 years, mean disease duration of 5 years, and mean EDSS at baseline ≤ 5.5. A total of 91% of patients had relapsing remitting multiple sclerosis, and 9% had a progressive form of multiple sclerosis with relapses. The median duration of treatment was 635, 627, and 631 days for AUBAGIO 7 mg, AUBAGIO 14 mg, and placebo, respectively.

There was a statistically significant reduction in ARR for patients who received AUBAGIO 7 mg or AUBAGIO 14 mg, 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 multiple sclerosis therapy, and baseline disease activity.

There was a statistically significant reduction in the relative risk of disability progression at week 108 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) in the AUBAGIO 14 mg group compared to placebo (see Table 2).

The effect of AUBAGIO on several magnetic resonance imaging (MRI) variables, including the total lesion volume of T2 and hypointense T1 lesions, was assessed in Study 1. The change in total lesion volume from baseline was significantly lower in the AUBAGIO 7 mg and AUBAGIO 14 mg groups than in the placebo group. Patients in both AUBAGIO 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

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>AUBAGIO 7 mg</th>
<th>AUBAGIO 14 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>365</td>
<td>358</td>
<td>363</td>
</tr>
<tr>
<td>Annualized relapse rate (p = 0.0002)</td>
<td>0.370</td>
<td>0.389</td>
<td>0.539</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>31%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Percent of patients remaining relapse-free at week 108</td>
<td>53.7%</td>
<td>56.5%</td>
<td>45.6%</td>
</tr>
</tbody>
</table>

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

Study 2 was a double-blind, placebo-controlled clinical trial that evaluated once daily doses of AUBAGIO 7 mg and AUBAGIO 14 mg for up to 40 months in patients with relapsing forms of multiple sclerosis. Patients were required to have a diagnosis of multiple sclerosis exhibiting a relapsing clinical course and to have experienced at least one relapse over the year preceding the trial, or at least two relapses over the two years preceding the trial. Patients were required not to have received any multiple sclerosis medication for at least three months before entering the trial, nor were these medications permitted during the trial. Neurological evaluations were to be performed at screening, every 12 weeks until completion, and after every suspected relapse. The primary end point was the ARR.

A total of 1165 patients received AUBAGIO 7 mg (n=407), AUBAGIO 14 mg (n=370), or placebo (n=388). Patients had a mean age of 38 years, a mean disease duration of 5 years, and a mean EDSS at baseline ≤ 5.5. A total of 96% of patients had relapsing remitting multiple sclerosis, and 4% had a progressive form of multiple sclerosis with relapses. The median duration of treatment was 552, 567, and 571 days for AUBAGIO 7 mg, AUBAGIO 14 mg, and placebo, respectively. The percentage of patients who completed the study treatment period was 67%, 66%, and 68% for AUBAGIO 7 mg, AUBAGIO 14 mg, and placebo, respectively.

There was a statistically significant reduction in the ARR for patients who received AUBAGIO 7 mg or AUBAGIO 14 mg compared to patients who received placebo (see Table 3). There was a consistent reduction of the ARR noted in subgroups defined by sex, age group, prior multiple sclerosis therapy, and baseline disease activity.

There was a statistically significant reduction in the relative risk of disability progression at week 108 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) in the AUBAGIO 14 mg group compared to placebo (see Table 3 and Figure 2).

Table 3. Clinical Results of Study 2

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>AUBAGIO 7 mg</th>
<th>AUBAGIO 14 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>407</td>
<td>370</td>
<td>388</td>
</tr>
<tr>
<td>Annualized relapse rate (p = 0.0183)</td>
<td>0.389</td>
<td>0.319</td>
<td>0.501</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>22%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Percent of patients remaining relapse-free at week 108 (p = 0.044)</td>
<td>58.2%</td>
<td>57.1%</td>
<td>46.8%</td>
</tr>
<tr>
<td>Hazard ratio (p = 0.0001)</td>
<td>9.94</td>
<td>0.69</td>
<td></td>
</tr>
</tbody>
</table>

Percent disability progression at week 108

Study 1: 21.7% (p = 0.084) 20.2% (p = 0.028) 27.3%

Study 2: 21.1% (p = 0.762) 15.8% (p = 0.044) 19.7%
The 14 mg tablet is pale blue to pastel blue, pentagonal film-coated tablet with dose strength
AUBAGIO is available as 7 mg and 14 mg tablets.

16 HOW SUPPLIED/STORAGE AND HANDLING
placebo (2.69), the difference being statistically significant for both (p=0.0234 and p=0.0052, respec-
tively) lower in patients treated with AUBAGIO 7 mg (1.06) and AUBAGIO 14 mg (0.98) as compared to
mean number of unique active lesions per brain MRI scan during the 36-week treatment period was
primary endpoint was the average number of unique active lesions/MRI scan during treatment. The
treatment initiation. A total of 179 patients were randomized to AUBAGIO 7 mg (n=61), AUBAGIO 14

group (61.7%).

Importance of Preventing Pregnancy
before starting AUBAGIO and for at least 6 months while they are taking AUBAGIO. Advise patients
that the use of some vaccines should be avoided during treatment with AUBAGIO and for at least 6 months after discontinuation.

Serious Allergic Reactions
Advises patients to discontinue AUBAGIO and seek immediate medical attention if any signs or
symptoms of a hypersensitivity reaction occur (see Contraindications (4) and Warnings and Precautions
(5.5)). Signs and symptoms include dyspnea, urticaria, and angioedema including lips, eyes, throat, and
tongue or skin rash.

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.

Increased Blood Pressure
Inform patients that AUBAGIO may increase blood pressure.

Lactation
Inform patients that it is not known whether this drug is present in human milk. Advise patients, if they
are considering breastfeeding, to discuss this with their healthcare provider to decide if they will take
AUBAGIO or breastfeed. Advise patients that they should not do both.

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:
  o within 6 months before you start taking AUBAGIO
  o 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:
  o nausea
  o vomiting
  o stomach pain
  o loss of appetite
  o tiredness
  o your skin or the whites of your eyes turn yellow
  o 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.
  o If you are a female, you should have a pregnancy test before you
start taking AUBAGIO. Use effective birth control during your

17 PATIENT COUNSELING INFORMATION
Advises the patient to read the FDA-approved patient labeling (Medication Guide).
A Medication Guide is required for distribution with AUBAGIO.

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.

Importance of Preventing Pregnancy
Inform patients that based on animal studies, AUBAGIO may cause fetal harm.

• Advise females of reproductive 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.

• Advise patients that if she suspects or confirms pregnancy, she should immediately inform her
physician.

• Advise men taking AUBAGIO and not wishing to father a child to use effective contraception to
minimize any possible risk to the fetus; their female partners should also use effective
contraception.
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 had an allergic reaction to AUBAGIO or a medicine called leflunomide
- 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 breastfeeding. You should not do both.

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:
  - 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.

- Allergic reactions, including serious skin problems. Tell your doctor if you have difficulty breathing, itching, swelling on any part of your body including in your lips, eyes, throat or tongue, or any skin problems such as rash or 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:
- headache
- diarrhea
- nausea
- hair thinning or loss (alopecia)
- increases in the results of blood tests to check your liver function

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 in 7 mg and 14 mg tablets: lactose monohydrate, corn starch, hydroxypropylcellulose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, and other coloring agents.

Information Services at 1-800-745-4447, option 2.

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