FAMILY PLANNING AND AUBAGIO® (teriflunomide)

INDICATION

AUBAGIO® (teriflunomide) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

IMPORTANT SAFETY INFORMATION

WARNING: HEPATOTOXICITY AND RISK OF TERATOGENICITY

- **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 6 months after starting AUBAGIO. If drug-induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or activated charcoal. AUBAGIO is contraindicated in patients with severe hepatic impairment. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.**
- **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 exposure lower than that in humans. Exclude pregnancy before the start of treatment with AUBAGIO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during AUBAGIO treatment and during an accelerated drug elimination procedure after AUBAGIO treatment. Stop AUBAGIO and use an accelerated drug elimination procedure if the patient becomes pregnant.**

Please see additional Important Safety Information on pages 4-5 and **Full Prescribing Information**, including **boxed WARNING**.

Once-daily AUBAGIO® (teriflunomide) 14 mg tablets

AUBAGIO is available in 14 mg and 7 mg tablets.

SAFETY IS OUR FIRST PRIORITY

Safety is one of the most important factors to consider when prescribing a drug for relapsing forms of multiple sclerosis (RMS), particularly for females of reproductive potential. AUBAGIO® (teriflunomide) has been shown to cause fetal harm in animal studies, so it is assumed that AUBAGIO may present a similar risk to the human fetus. The following points are designed to help you talk to your patients about AUBAGIO and the importance of preventing pregnancy during therapy.

Use of effective contraception during AUBAGIO therapy

- AUBAGIO is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception
- The safety of AUBAGIO has not been studied in pregnant women
- Before starting AUBAGIO, pregnancy must be excluded; similarly, pregnancy should be avoided during treatment
- Females of reproductive potential should use effective contraception during AUBAGIO therapy
- AUBAGIO has been detected in human semen. Male patients taking AUBAGIO should also use effective contraception
- If a patient has any reason to suspect pregnancy, she should inform her health care professional (HCP) immediately. **Pregnant women should not use AUBAGIO**

If patients become or want to become pregnant, the elimination of the drug can be accelerated

- If a patient becomes pregnant during AUBAGIO therapy, there is an accelerated elimination procedure that reduces plasma drug levels by >98% within 11 days. Blood levels <0.02 mcg/mL are thought to pose minimal risk to the fetus*
  - After discontinuation of AUBAGIO and use of the accelerated elimination procedure, including verification of drug levels, patients should be referred to an obstetrician/gynecologist (OB/GYN) for further evaluation and counseling
  - Use of the accelerated elimination procedure may potentially result in return of disease activity in patients who were responding to AUBAGIO treatment
- Women who become pregnant while taking AUBAGIO may enroll in the **AUBAGIO Pregnancy Registry** by calling **1-800-745-4447, option 2.** The purpose of the registry is to collect information on the safety of the therapy during pregnancy
- If a patient wants to become pregnant, she should discontinue AUBAGIO therapy and undergo the accelerated elimination procedure. Effective contraception should be continued until the accelerated elimination procedure is complete and plasma concentrations <0.02 mcg/mL are verified via a separate lab test
- Confirmation of elimination is available via a LabCorp assay that is paid for by Sanofi Genzyme. Sanofi Genzyme will pay for the blood draw when performed by LabCorp but cannot pay for the blood draw in an HCP's office. Forms to set up an account with LabCorp are available from your Sanofi Genzyme representative or by contacting *MS One to One*® at 1-855-MSOne2One (1-855-676-6326). Once your account is set up, you will be provided with assay requisition forms and can order the assay for your patients as needed

Begin the dialogue

- Have your patient give the following page to her OB/GYN or other HCP involved in reproductive health decisions. You may also fax the form directly to the HCP's office, making sure to comply with HIPAA guidelines

For additional resources and support

- Visit AubagioHCP.com or contact *MS One to One*® at 1-855-MSOne2One (1-855-676-6326)

*Teriflunomide is eliminated slowly from the plasma. Without accelerated elimination, it takes an average of 8 months, but because of individual variations in drug clearance it may take up to 2 years, to reach plasma concentrations of <0.02 mcg/mL.

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FOR OBSTETRICIAN/GYNECOLOGIST OR INTERNIST USE

Patient name: _____ Date of birth: _____

Referring neurologist: _____ Phone number: _____

AT SANOFI GENZYME, WE UNDERSTAND THAT YOUR PATIENTS' SAFETY MATTERS

Your patient has been prescribed AUBAGIO® (teriflunomide) for the treatment of relapsing forms of multiple sclerosis (RMS). AUBAGIO has been shown in animal studies to cause fetal harm, so it is assumed that it presents a similar risk to the human fetus. We want to help ensure that you and your patients understand the importance of preventing pregnancy during AUBAGIO therapy and the safety measures in place in the event of inadvertent pregnancy.

The following points are designed to help you speak with your patients about preventing pregnancy during AUBAGIO therapy:

Females of reproductive potential can use AUBAGIO if they use effective contraception

Pregnancy must be avoided during AUBAGIO therapy

- Females of reproductive potential **should use effective contraception to prevent pregnancy while using AUBAGIO**
- Before starting AUBAGIO, pregnancy must be excluded; similarly, pregnancy should be avoided during treatment
- Men taking AUBAGIO should also use effective contraception
- The type or dose of oral contraceptives used in combination with AUBAGIO should be considered because of increased ethinylestradiol and levonorgestrel levels following repeated doses of AUBAGIO

Pregnant women should not use AUBAGIO

- AUBAGIO is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception
- If your patient has any reason to suspect pregnancy, she should inform you and her other health care professionals (HCPs) immediately
- Nursing mothers should not use AUBAGIO

If patients become or want to become pregnant, the elimination of the drug can be accelerated

- If your patient becomes pregnant during AUBAGIO therapy, there is an accelerated elimination procedure that reduces plasma drug levels by >98% within 11 days. Blood levels <0.02 mcg/mL are thought to pose minimal risk to the fetus
  - — Teriflunomide is eliminated slowly from the plasma. Without accelerated elimination, it takes an average of 8 months, or up to 2 years because of individual variations in drug clearance, to reach plasma concentrations <0.02 mcg/mL
- Women who become pregnant during AUBAGIO therapy may enroll in the **AUBAGIO Pregnancy Registry** by calling **1-800-745-4447, option 2.** The purpose of the registry is to collect information on the safety of the therapy during pregnancy
- If your patient wants to become pregnant, she should continue to use effective contraception until she has discontinued AUBAGIO and undergone the accelerated elimination procedure (including verification that drug levels are <0.02 mcg/mL)
- Confirmation of elimination is available via a LabCorp assay that is paid for by Sanofi Genzyme. Sanofi Genzyme will pay for the blood draw when performed by LabCorp but cannot pay for the blood draw in an HCP's office. Forms to set up an account with LabCorp are available from your Sanofi Genzyme representative or by contacting *MS One to One*® at 1-855-MSOne2One (1-855-676-6326). Once your account is set up, you will be provided with assay requisition forms and can order the assay for your patients as needed

Reference: AUBAGIO (teriflunomide) [package insert]. Cambridge, MA: Genzyme Corporation; November 2016.

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- **Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for 6 months after starting AUBAGIO. If drug-induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or activated charcoal. AUBAGIO is contraindicated in patients with severe hepatic impairment. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.**
- **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 exposure lower than that in humans. Exclude pregnancy before the start of treatment with AUBAGIO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during AUBAGIO treatment and during an accelerated drug elimination procedure after AUBAGIO treatment. Stop AUBAGIO and use an accelerated drug elimination procedure if the patient becomes pregnant.**

CONTRAINDICATIONS

- Patients with severe hepatic impairment.
- Pregnant women and females of reproductive potential not using effective contraception.
- Patients with a history of hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in AUBAGIO.
- Co-administration with leflunomide.

WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Patients with pre-existing acute or chronic liver disease, or those with serum ALT >2 times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with AUBAGIO. In clinical trials, if ALT elevation was >3 times the ULN on 2 consecutive tests, patients discontinued AUBAGIO and underwent accelerated elimination. Consider additional monitoring if co-administering AUBAGIO with other potentially hepatotoxic drugs; monitor patients who develop symptoms suggestive of hepatic dysfunction (eg, unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine).
- **Teratogenicity:** AUBAGIO may cause fetal harm when administered in pregnant women. Teratogenicity and embryo-fetal lethality occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than that in humans at the maximum human recommended dose of 14 mg/day. AUBAGIO is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception. Women who become pregnant while taking AUBAGIO may enroll in the AUBAGIO pregnancy registry by calling 1-800-745-4447, option 2.
- **Procedure for Accelerated Elimination of Teriflunomide:** Teriflunomide is eliminated slowly from the plasma—it takes an average of 8 months, or up to 2 years, to reach plasma concentrations <0.02 mcg/mL. Elimination may be accelerated by administration of cholestyramine or activated charcoal, but this may cause disease activity to return in patients who were responding to AUBAGIO.

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4 Full Prescribing Information, including **boxed WARNING**.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Bone Marrow Effects/Immunosuppression Potential/Infections:** Decreases in white blood cell counts, mainly of neutrophils and lymphocytes, and platelets have been reported with AUBAGIO. Thrombocytopenia, including rare cases with platelet counts less than 50,000/mm^3, has been reported in the postmarketing setting. Obtain a complete blood cell count within 6 months before starting treatment, with further monitoring based on signs and symptoms of bone marrow suppression. AUBAGIO is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe uncontrolled infections. Tuberculosis (TB) has been observed in clinical studies of AUBAGIO. Before starting treatment, screen patients for latent TB infection with a tuberculin test. Treatment in patients with acute or chronic infections should not be started until the infection(s) is resolved. Administration of live vaccines is not recommended. The risk of malignancy, particularly lymphoproliferative disorders, or infection may be increased with the use of some medications with immunosuppressive potential, including teriflunomide.
- **Hypersensitivity and Serious Skin Reactions:** AUBAGIO can cause anaphylaxis and severe allergic reactions. Signs and symptoms have included dyspnea, urticaria, and angioedema including lips, eyes, throat, and tongue. Cases of serious skin reactions, including Stevens-Johnson syndrome and a fatal case of toxic epidermal necrolysis, have been reported with AUBAGIO. Very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms have also been reported with leflunomide. If a severe skin reaction develops with AUBAGIO, stop treatment and begin accelerated elimination. In such cases, patients should not be re-exposed to teriflunomide.
- **Peripheral Neuropathy:** Peripheral neuropathy, including polyneuropathy and mononeuropathy, has been reported with AUBAGIO. Age >60 years, concomitant neurotoxic medications, and diabetes may increase the risk. If peripheral neuropathy is suspected, consider discontinuing treatment and performing accelerated elimination.
- **Increased Blood Pressure:** Blood pressure increases and hypertension have occurred with AUBAGIO. Measure blood pressure at treatment initiation and manage any elevations during treatment.
- **Respiratory Effects:** Interstitial lung disease (ILD), including acute interstitial pneumonitis, has been reported with AUBAGIO. ILD may be fatal and may occur acutely at any time during therapy with a variable clinical presentation. If discontinuation of the drug is necessary, consider initiation of an accelerated elimination procedure.

Adverse Reactions: The most frequent adverse reactions (≥10% and ≥2% greater than placebo) with AUBAGIO 7 mg and 14 mg and placebo, respectively, were headache (18% and 16% vs 15%), ALT increased (13% and 15% vs 9%), diarrhea (13% and 14% vs 8%), alopecia (10% and 13% vs 5%), and nausea (8% and 11% vs 7%).

Drug Interactions: Monitor patients when teriflunomide is coadministered with warfarin, or with drugs metabolized by CYP1A2, CYP2C8, substrates of OAT3 transporters, substrates of BCRP, or OATP1B1/1B3 transporters.

Use in Specific Populations: Women who wish to become pregnant should discontinue AUBAGIO and undergo an accelerated elimination procedure. Use of effective contraception should be continued until plasma concentrations of teriflunomide are <0.02 mcg/mL. Nursing mothers should not use AUBAGIO. AUBAGIO is detected in human semen. To minimize any possible fetal risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue therapy and either undergo accelerated elimination or verify plasma teriflunomide concentration is <0.02 mcg/mL.

For additional resources and support, please visit AubagioHCP.com or contact *MS One to One*® at 1-855-MSOne2One (1-855-676-6326)

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SANOFI GENZYME

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