

FOR YOUR PATIENTS WITH RELAPSING FORMS OF MS

INITIATING ORAL AUBAGIO® (teriflunomide) THERAPY

INDICATION

AUBAGIO® (teriflunomide) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION

WARNING: HEPATOTOXICITY AND EMBRYOFETAL TOXICITY

- 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 embryoletality 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.

Once-daily
AUBAGIO[®]
(teriflunomide) 14 mg
tablets

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

AUBAGIO is available in 14 mg and 7 mg tablets.

INITIATING ORAL AUBAGIO THERAPY

One tablet, once daily

- AUBAGIO® (teriflunomide) is taken orally once daily, with or without food

Monitoring liver enzymes

- AUBAGIO is contraindicated in patients with severe hepatic impairment
- Obtain transaminase and bilirubin levels within 6 months before starting AUBAGIO and monitor alanine aminotransferase (ALT) levels monthly for at least 6 months after starting AUBAGIO

Considerations for females of reproductive potential taking AUBAGIO

Before starting AUBAGIO therapy

- AUBAGIO is contraindicated in pregnant women and females of reproductive potential who are not using effective contraception. Exclude pregnancy and confirm use of effective contraception
- Counsel patients fully on the potential for serious risks to the fetus

During AUBAGIO therapy

- Counsel patients to avoid pregnancy. If there is any reason to suspect pregnancy, patients should notify their health care professional (HCP) immediately for pregnancy testing
- If a patient becomes pregnant or wants to become 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, based on animal data*
- 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

Considerations for male patients taking AUBAGIO

- Instruct patients and their female partners to use effective contraception to minimize any possible risk
- AUBAGIO is detected in human semen. Animal studies to specifically evaluate the risk of male-mediated fetal toxicity have not been conducted
- If patients wish to father a child, discontinue AUBAGIO therapy and either administer the accelerated elimination procedure or wait until plasma concentrations of teriflunomide are <0.02 mcg/mL*

Monitoring for infection

- Obtain a complete blood count (CBC) within 6 months before starting treatment with AUBAGIO and as clinically indicated. AUBAGIO is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections
- Patients with active acute or chronic infections should not start treatment until the infection is resolved
- Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection with a tuberculin skin or blood test

Other assessments

- Check blood pressure before starting AUBAGIO treatment and periodically thereafter

*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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Patient name: _____

Therapy start date: _____

ROUTINE MONITORING RECOMMENDED:

Before starting AUBAGIO® (teriflunomide) therapy

- Complete the AUBAGIO Start Form
- Check transaminase and bilirubin levels (within 6 months before starting therapy)
- Exclude pregnancy and confirm use of effective contraception
- Counsel patients on the potential for serious risk to the fetus and use of effective contraception in females of reproductive potential
- Obtain a complete blood count (CBC) (within 6 months before starting therapy)
- Screen for latent tuberculosis infection
- Check baseline blood pressure

During AUBAGIO therapy

- Monitor alanine aminotransferase (ALT) levels monthly (for 6 months)
- Check blood pressure periodically
- Counsel patients to continue use of effective contraception during therapy

AUBAGIO is contraindicated in patients with severe hepatic impairment, in pregnant women, in females of reproductive potential who are not using effective contraception, in patients with a history of hypersensitivity to teriflunomide, its inactive ingredients or leflunomide, or who are currently taking leflunomide.

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

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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).
- **Embryofetal Toxicity:** AUBAGIO may cause fetal harm when administered in pregnant women. Teratogenicity and embryofetal 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. Exclude pregnancy before starting 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 (AEP) after AUBAGIO treatment. If a woman becomes pregnant while taking AUBAGIO, stop treatment, apprise patient of the potential risk to a fetus, and perform an AEP to achieve an AUBAGIO plasma concentration of <0.02 mg/L. Upon discontinuing AUBAGIO, it is recommended all females of reproductive potential undergo an AEP. Women receiving AUBAGIO who wish to become pregnant must discontinue AUBAGIO and undergo an AEP, until plasma concentrations of AUBAGIO are <0.02 mg/L. Men wishing to father a child should also stop AUBAGIO and either undergo an AEP or wait until plasma concentration of AUBAGIO is <0.02 mg/L. Women who become pregnant while taking AUBAGIO may enroll in the AUBAGIO pregnancy registry by calling 1-800-745-4447, option 2.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **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.
- **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 $50,000/\text{mm}^3$, 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 ($\geq 10\%$ and $\geq 2\%$ 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 should not breastfeed during treatment with AUBAGIO.

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