A GUIDE TO THE **ACCELERATED ELIMINATION PROCEDURE** FOR 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 8-9 and **Full Prescribing Information**, including **boxed WARNING**.

Once-daily AUBAGIO® (teriflunomide) 14 mg tablets

AUBAGIO is available in 14 mg and 7 mg tablets.

WHAT IS THE ACCELERATED ELIMINATION PROCEDURE?

Drug elimination processes can be used in certain situations to reduce plasma concentrations of some drugs. A reliable accelerated elimination procedure is available for AUBAGIO® (teriflunomide), indicated for the treatment of relapsing forms of multiple sclerosis.[1]

WHEN IS THE ACCELERATED ELIMINATION PROCEDURE REQUIRED?

The accelerated elimination procedure should be used after discontinuation of AUBAGIO when[1]:

- Drug-induced liver injury is suspected
- Pregnancy occurs during AUBAGIO therapy (use of this procedure may decrease risk to the fetus)
- A patient taking AUBAGIO wants to become pregnant or father a child
- Accelerated removal of drug is clinically desired (e.g., overdose or serious skin reactions)

The procedure is also recommended after discontinuation of therapy in females of reproductive potential or in the event of clinically significant toxicity.[1]

WHY IS ACCELERATED ELIMINATION REQUIRED IN THESE CASES?

AUBAGIO® (teriflunomide) is eliminated slowly from the plasma. Without accelerated elimination, it takes an average of 8 months, or up to 2 years in some patients, to reach plasma concentrations <0.02 mcg/mL (<0.02 mg/L).[1]

WHAT IS THE ACCELERATED ELIMINATION REGIMEN FOR AUBAGIO?

Recommended procedures[1]:

- Administration of cholestyramine 8 g every 8 hours for 11 days
  - — If cholestyramine 8 g every 8 hours is not well tolerated, cholestyramine 4 g every 8 hours can be used
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days

If tolerability is an issue, administration does not need to occur on consecutive days unless there is an overriding need to lower teriflunomide plasma concentrations rapidly.[1]

Accelerated elimination regimens for AUBAGIO[1]

Agent	Dosage	Duration of treatment
Cholestyramine	8 g q8h	11 days
Cholestyramine	4 g q8h	11 days
Activated charcoal	50 g q12h	11 days

(*Continued on next page.*)

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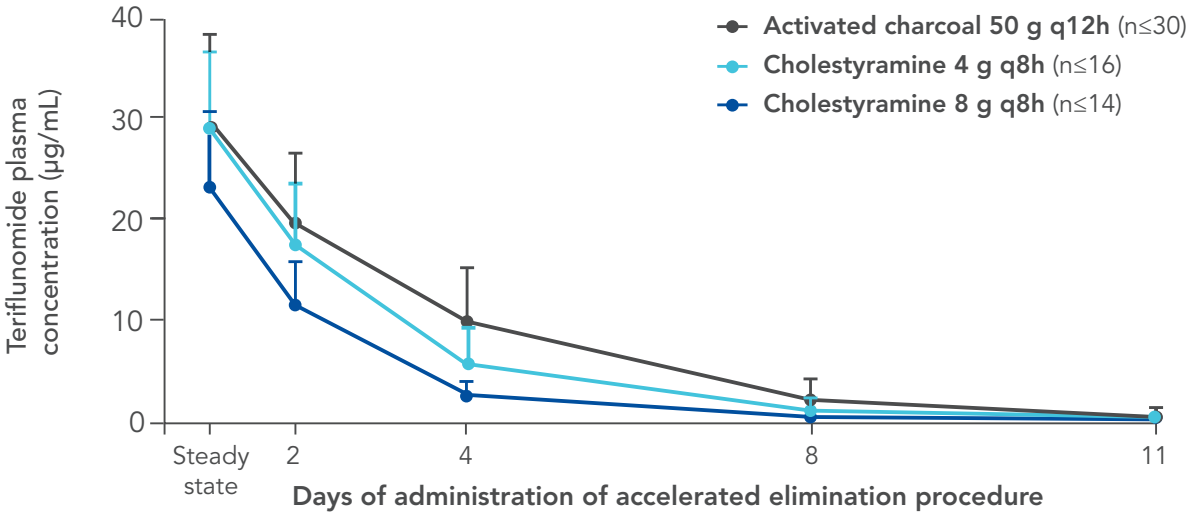
WHAT IS THE ACCELERATED ELIMINATION REGIMEN FOR AUBAGIO® (teriflunomide)? *(continued)*

After 11 days of cholestyramine or activated charcoal administration, plasma concentrations of teriflunomide are reduced by >98%.[1] Accelerated elimination using cholestyramine appears to be more rapid than charcoal.[2] In patients who are pregnant or wish to become pregnant, or in males who wish to father a child, a blood sample should be taken to confirm that blood levels are <0.02 mcg/mL, a level expected to have minimal risk to the fetus.[1]

Plasma concentrations of teriflunomide after accelerated elimination[2]

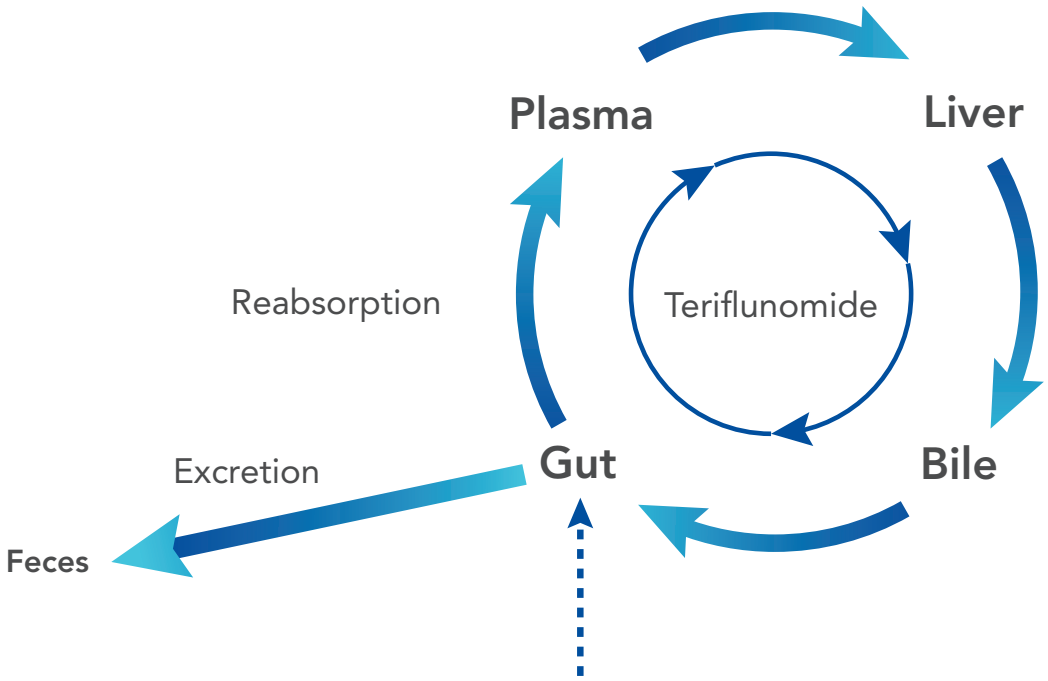


- At the end of 11 days, each regimen successfully accelerated teriflunomide elimination[2]

HOW DOES ACCELERATED ELIMINATION OF AUBAGIO WORK?

AUBAGIO® (teriflunomide) normally undergoes enterohepatic recycling,[2] a process in which bile acids and other substances excreted by the liver are absorbed by the intestinal mucosa and returned to the liver via the portal vein.

Cholestyramine and activated charcoal bind and sequester teriflunomide in the small intestine and prevent it from being reabsorbed, thus accelerating its elimination.[2]



Cholestyramine and activated charcoal sequester teriflunomide in the small intestine, preventing reabsorption and enterohepatic recirculation[2]

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ARE THERE ANY ADVERSE EVENTS ASSOCIATED WITH THE ACCELERATED ELIMINATION PROCEDURE?

In some cases, patients may experience mild to moderate gastrointestinal side effects such as upset stomach or nausea.[2] Consult the product information for cholestyramine or activated charcoal for more information.

Use of the accelerated elimination procedure may potentially result in return of disease activity if the patient had been responding to AUBAGIO® (teriflunomide) treatment.[1]

DO I NEED TO CONFIRM THAT THE DRUG HAS BEEN SUCCESSFULLY ELIMINATED?

When the accelerated elimination procedure is used for women who are or wish to become pregnant, or men who wish to father a child, a blood test is used to confirm that plasma drug concentrations are reduced to <0.02 mcg/mL, a level expected to have minimal risk to the fetus.[1]

Confirmation of teriflunomide plasma levels via an assay is only recommended for women who are or wish to become pregnant, or men wishing to father a child.[1]

IS THERE ANYTHING I SHOULD KNOW ABOUT HOW TO PRESCRIBE CHOLESTYRAMINE?

It is recommended that patients take other medications at least 1 hour before or 4 to 6 hours after taking cholestyramine.[3]

IF I DO NEED TO CONFIRM MY PATIENT'S PLASMA LEVELS OF TERIFLUNOMIDE, HOW DO I OBTAIN THE ASSAY?

Confirmation of teriflunomide plasma levels is available via a LabCorp assay that is paid for by Sanofi Genzyme. In addition, Sanofi Genzyme will pay for the blood draw when performed by LabCorp but cannot pay for the blood draw in a health care professional'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.

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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.

(*Continued on next page.*)

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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.

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References: 1. AUBAGIO (teriflunomide) [package insert]. Cambridge, MA: Genzyme Corporation; November 2016. **2.** Miller A, Turpault S, Menguy-Vacheron F. Rapid elimination procedure of teriflunomide with cholestyramine or activated charcoal. Poster presented at: 17th Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis; June 1-2, 2012; San Diego, CA. Poster P10. **3.** Questran (cholestyramine) [package insert]. Spring Valley, NY: Par Pharmaceutical Companies, Inc; April 2014.

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