

FOR RMS PATIENTS ON AUBAGIO, ELIMINATION CAN BE ACCELERATED¹

A step-by-step guide to the accelerated elimination procedure for your AUBAGIO® (teriflunomide) patients and your office



How the accelerated elimination procedure works for your patients



How the accelerated elimination procedure works for your office

RMS=relapsing forms of multiple sclerosis.

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 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 throughout and **Full Prescribing Information**, including **boxed WARNING**.

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

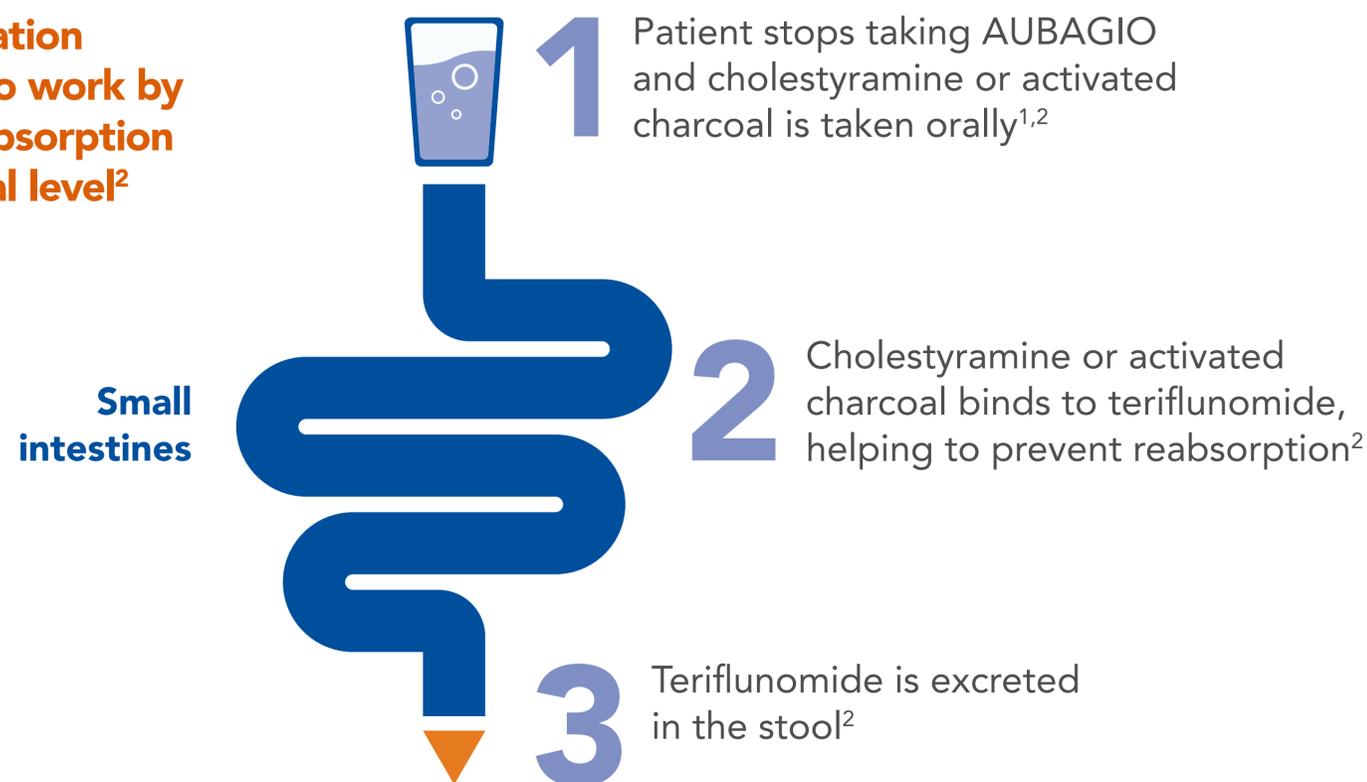
AUBAGIO is available in 14 mg and 7 mg tablets.

THE ACCELERATED ELIMINATION PROCEDURE: WHAT IT IS AND HOW IT WORKS

The accelerated elimination is a procedure that can quickly and successfully eliminate AUBAGIO® (teriflunomide) for a variety of clinical situations²

- Enables HCPs to lower the plasma levels of AUBAGIO in 11 days to <0.02 mg/L (<20 mg/mL) when desired or required¹
- It may not be necessary to eliminate AUBAGIO when switching patients to interferon or glatiramer acetate^{1*}

The accelerated elimination procedure is thought to work by interruption of the reabsorption process at the intestinal level²



Dosing regimen

- **Cholestyramine** 8 g 3 times daily^{1,2}
 - If cholestyramine 8 g every 8 hours is not well tolerated, cholestyramine 4 g every 8 hours can be used¹
- **Activated charcoal** 50 g 2 times daily (oral powder)^{1,2}

*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.¹

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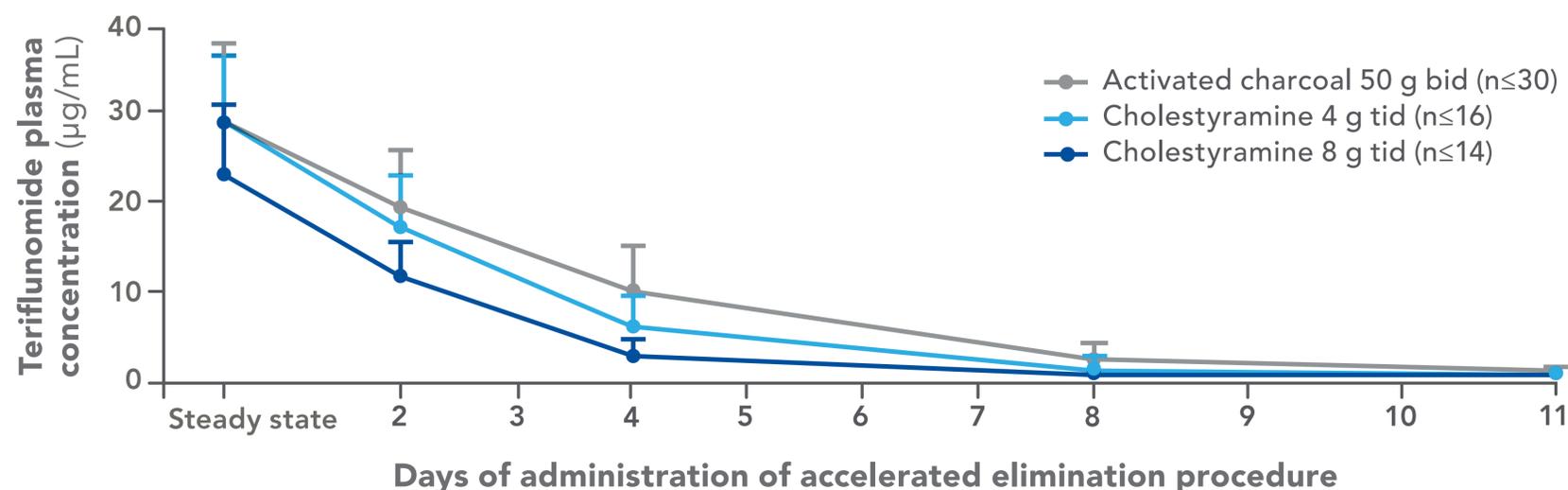
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THE ACCELERATED ELIMINATION TIMELINE

There are two accelerated elimination regimens available; both eliminated AUBAGIO® (teriflunomide) by 11 days^{1,2}

Plasma concentrations of teriflunomide after accelerated elimination²



- Without the accelerated elimination procedure, it takes 8 months on average to reach plasma levels of <0.02 mg/L (<20 mg/mL), although because of individual variations in drug clearance, it may take as long as 2 years¹
- 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 rapidly¹



Cholestyramine 8 g 3 times a day^{1,3}

91%

decrease in plasma levels at the end of day 3³

>98%

decrease in plasma levels at the end of day 11³

IMPORTANT SAFETY INFORMATION (continued)

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.

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FREQUENTLY ASKED QUESTIONS

1. When is the accelerated elimination procedure required?

- A.** The accelerated elimination procedure should be used after discontinuation of AUBAGIO® (teriflunomide) when^{1,2}:
- Drug-induced liver injury is suspected
 - Pregnancy occurs during AUBAGIO therapy
 - A patient taking AUBAGIO wants to become pregnant or father a child
 - Accelerated removal of drug is clinically desired

2. Do I need to confirm that the drug has been successfully eliminated?

- A.** Confirmation of teriflunomide plasma levels via an assay is recommended for women who are or wish to become pregnant, or men wishing to father a child. A blood test following the accelerated elimination procedure confirms the plasma drug concentrations are reduced to <0.02 mg/L (<20 mg/mL), a level expected to have minimal risk to the fetus, based on animal data.¹

3. How do I confirm that the drug has been successfully eliminated?

- A.** Confirmation of teriflunomide plasma levels is available via your preferred laboratory or a LabCorp assay following the accelerated elimination procedure and subsequent blood draw.

4. Does Sanofi Genzyme pay for the lab assay and blood draw?

- A.** The blood draw and assay are paid for by Sanofi Genzyme only when they are performed through the Sanofi Genzyme/LabCorp program. Sanofi Genzyme does not cover blood draws performed in the health care professional's office or through other laboratories.

5. Do I need a LabCorp account?

- A.** Yes. If you don't have one already, you will want to set up a LabCorp account *prior* to patients' testing. It may take up to 5-7 business days to set up an account with LabCorp and receive a lab requisition form. Reach out to *MS One to One*® at 1-855-MSOne2One (1-855-676-6326) today to set up your LabCorp account.

6. How do I acquire the assay requisition form?

- A.** Your office will need to contact LabCorp at LCAMSSupport@LabCorp.com to obtain an assay requisition form after an account has been set up.

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5 STEPS FOR YOUR OFFICE TO GET STARTED



Step 1

Contact LabCorp at LCAMSSupport@LabCorp.com to obtain an assay requisition form



Step 4

Send plasma samples to your office, preferred laboratory, or LabCorp



Step 2

Prescribe cholestyramine or activated charcoal. Patient begins regimen



Step 5

Detailed results with plasma concentrations will be sent to you from your laboratory by usual means, or from LabCorp via fax or through their portal (Beacon)



Step 3

Have patient's blood drawn for analysis in the office, at the preferred laboratory, or at LabCorp on day 11 of the patient's accelerated elimination regimen

IMPORTANT SAFETY INFORMATION (continued) 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).

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- Co-administration with leflunomide.

WARNINGS AND PRECAUTIONS

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- **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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AUBAGIO is available in 14 mg and 7 mg tablets.

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/mm³, 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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IN THE TREATMENT OF RMS,
**THE ACCELERATED ELIMINATION
PROCEDURE IS AVAILABLE WHEN
YOUR AUBAGIO PATIENT NEEDS IT**

**SANOFI GENZYME IS COMMITTED TO SUPPORTING PATIENTS ON AUBAGIO. TALK TO YOUR
SANOFI GENZYME REPRESENTATIVE TODAY**

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

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References: **1.** AUBAGIO (teriflunomide) [package insert]. Cambridge, MA: Genzyme Corporation. **2.** Freedman MS. Teriflunomide in relapsing multiple sclerosis: therapeutic utility. *Ther Adv Chronic Dis.* 2013;4:192-205. **3.** Data on file, Sanofi Genzyme.

SANOFI GENZYME 

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SAUS.AUBA.19.07.3855a (10/19)

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