FOR RMS PATIENTS ON AUBAGIO, ELIMINATION CAN BE ACCELERATED

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

- Clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, has been reported in patients treated with AUBAGIO in the postmarketing setting. Concomitant use of AUBAGIO with other 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.
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 situations\(^2\)

- Enables HCPs to lower the plasma levels of AUBAGIO in 11 days to \(<0.02\text{ mg/L} (<20\text{ mg/mL})\) when desired or required\(^1\)
- 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 level\(^2\)**

1. Patient stops taking AUBAGIO and cholestyramine or activated charcoal is taken orally\(^1,2\)

2. Cholestyramine or activated charcoal binds to teriflunomide, helping to prevent reabsorption\(^2\)

3. Teriflunomide is excreted in the stool\(^2\)

\(^*\)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.\(^1\)

**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 used\(^1\)
- **Activated charcoal** 50 g 2 times daily (oral powder)\(^1,2\)


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

**Plasma concentrations of teriflunomide after accelerated elimination**\textsuperscript{2}

- 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 years\textsuperscript{1}
- 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\textsuperscript{1}

**THE ACCELERATED ELIMINATION TIMELINE**

**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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1. When is the accelerated elimination procedure required?
   A. The accelerated elimination procedure should be used after discontinuation of AUBAGIO® (teriflunomide) when\(^1\):  
      • Drug-induced liver injury or serious skin reaction are 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\(^\circledast\) 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.
5 STEPS FOR YOUR OFFICE TO GET STARTED

Step 1
Contact LabCorp at LCAMSSupport@LabCorp.com to obtain an assay requisition form

Step 2
Prescribe cholestyramine or activated charcoal. Patient begins regimen

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

Step 4
Send plasma samples to your office, preferred laboratory, or LabCorp

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)

IMPORTANT SAFETY INFORMATION (continued)
WARNING AND PRECAUTIONS

- **Hepatotoxicity:** Clinically significant liver injury, which could be life-threatening, can occur at any time during treatment with AUBAGIO. 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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• 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

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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 who become pregnant while taking AUBAGIO may enroll in the AUBAGIO pregnancy registry by calling 1-800-745-4447, option 2.

Please see Full Prescribing Information, including boxed WARNING.
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 immunsuppressive potential, including teriflunomide.

- **Hypersensitivity Reactions**: AUBAGIO can cause anaphylaxis and severe allergic reactions. Signs and symptoms have included dyspnea, urticaria, and angioedema including lips, eyes, throat, and tongue. Inform patients of the signs and symptoms of anaphylaxis and angioedema.

- **Serious Skin Reactions**: Cases of serious skin reactions, sometimes fatal, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with AUBAGIO. Fatal outcomes were reported in one case of TEN and one case of DRESS. Inform patients of the signs and symptoms of a serious skin reaction and instruct them to discontinue AUBAGIO and seek immediate medical care. Unless the reaction is clearly not drug-related, discontinue AUBAGIO and begin accelerated elimination immediately. In such cases, patients should not be re-exposed to teriflunomide.

- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**: DRESS, also known as multiorgan hypersensitivity, has occurred with AUBAGIO. One fatal case of DRESS that occurred within 34 days of initiation of AUBAGIO treatment has been reported in the postmarketing setting. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (eg, fever, lymphadenopathy) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately.

- **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 should not breastfeed during treatment with AUBAGIO.

Please see [Full Prescribing Information](#), including boxed WARNING.
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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AUBAGIO is available in 14 mg and 7 mg tablets.