

How AUBAGIO works

Understand the proposed mechanism of action for AUBAGIO[®] (teriflunomide)

Research implicates both T and B cells in the pathophysiology of multiple sclerosis, or MS. In MS, myelin-specific autoreactive lymphocytes, which are first activated in the peripheral immune system, cross the blood-brain barrier and attack neurons in the central nervous system, or CNS.^{1,2}

AUBAGIO, or teriflunomide, is an oral immunomodulator that is indicated for the treatment of people with relapsing forms of MS.³

Research supports that AUBAGIO inhibits the proliferation of activated T and B lymphocytes in the periphery. Through this cytostatic effect, AUBAGIO appears to limit the number of autoreactive lymphocytes that can contribute to MS disease activity.^{2,4}

While both resting and activated lymphocytes require pyrimidine for basic homeostatic metabolism, they rely on different pathways to satisfy this demand. Research demonstrates that resting and slowly dividing lymphocytes can recycle, or salvage, pyrimidines, which is sufficient to meet the metabolic needs of these cells. However, rapidly proliferating lymphocytes, like activated T and B cells, have a demand for pyrimidines that exceeds the capacity of the salvage pathway, so they must synthesize new pyrimidines via the *de novo* pathway to meet that demand.⁵

AUBAGIO has been demonstrated to inhibit dihydroorotate dehydrogenase, or DHODH, a key mitochondrial enzyme in the *de novo* pyrimidine synthesis pathway required by rapidly dividing cells.^{3,5}

Results from preclinical and animal model studies suggest that by blocking the *de novo* pyrimidine synthesis pathway, AUBAGIO exerts a cytostatic effect on activated proliferating T and B cells in the periphery. These cells are thought to be responsible for the damaging inflammatory process of MS when they migrate into the CNS.²

Through this effect, AUBAGIO is thought to limit rapid proliferation associated with autoreactive immune responses and therefore has the potential to reduce the number of activated pathogenic T and B cells available to migrate into the CNS.^{2,5}

Since the pyrimidine salvage pathway is unaffected by AUBAGIO, basic homeostatic cell functions of resting and slowly dividing lymphocytes appear to be preserved.^{2,5}

Understanding how AUBAGIO works:

AUBAGIO represents a promising addition to the MS treatment armamentarium.

The exact MOA of this agent and the way it exerts its therapeutic effect on MS is unknown.³

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.

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.
- **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 (≥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.

Please see Full Prescribing information, including **boxed WARNING**.

References:

1. Ireland S, Monson N. Potential impact of B cells on T cell function in multiple sclerosis. *Mult Scler Int*. 2011;2011:(423971):1-9.
2. Gold R, Wolinsky JS. Pathophysiology of multiple sclerosis and the place of teriflunomide. *Acta Neurol Scand*. 2011;124(2):75-84.
3. AUBAGIO (teriflunomide) [package insert]. Cambridge, MA: Genzyme Corporation; November 2016.
4. Li L, Liu J, Delohery T, Jones C. The effects of teriflunomide on lymphocyte subpopulations in human peripheral blood mononuclear cells. Poster presented at: 5th Joint Triennial Congress ofECTRIMS/ACTRIMS; October 19-22, 2011; Amsterdam, the Netherlands. Poster P938.
5. Claussen MC, Korn T. Immune mechanisms of new therapeutic strategies in MS: teriflunomide. *Clin Immunol*. 2012;142(1):49-56.

