Drug Monograph

Drug/Drug Class:	**Aubagio™ (teriflunomide) tablet / pyrimidine synthesis inhibitor**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each 7 mg of Aubagio™ tablet contains 7 mg of teriflunomide and each 14 mg tablet of Aubagio™ contains 14 mg of teriflunomide. Genzyme Corporation 500 Kendall Street Cambridge, MA 02142 A SANOFI COMPANY
Summary of Findings:	Teriflunomide, the primary active metabolite of leflunomide, is an immunomodulatory agent with anti-inflammatory properties. It is a once daily pyrimidine synthesis inhibitor that has demonstrated efficacy for the treatment of patients with relapsing forms of multiple sclerosis (RMS).
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ No PA Required ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Multiple Sclerosis affects about 400,000 people in the United States. There are 4 basic presentations of MS, the most common being the relapsing form. The strategies for treating MS include reducing the number of attacks, reducing the number of lesions observed on MRI scans, slowing the progression of disability, and improving the speed of recovery.

Dosage Form(s) [1]

Each 7 mg Aubagio™ tablet contains 7 mg of teriflunomide and each 14 mg Aubagio™ tablet contains 14 mg of teriflunomide.

Manufacturer

Genzyme Corporation 500 Kendall Street Cambridge, MA 02142
A SANOFI COMPANY

Indication(s) [1]

Aubagio is FDA approved to treat patients with relapsing forms of multiple sclerosis (MS).

Clinical Efficacy[1-9] (mechanism of action/pharmacology, comparative efficacy)

Teriflunomide, the primary active metabolite of leflunomide, is an immunomodulatory agent with anti-inflammatory properties. It inhibits dihydroorotate dehydrogenase, which is a mitochondrial enzyme involved in de novo pyrimidine synthesis.

PHARMACOKINETICS

	AUBAGIO
Protein Binding	> 99%
Volume of Distribution IV	11L
Metabolism	Hepatic primarily hydrolysis; secondary pathways involve oxidation, N-acetylation and sulfate conjugation
Excretion	Feces 37.5%; Urine 22.6%
Half Life (median)	18 to 19 days

EFFICACY (1-9) SUMMARY

The approval of Aubagio was primarily based upon a double-blind, placebo-controlled clinical trial (TEriflunomide Multiple Sclerosis Oral; TEMSO) involving 1088 patients with RMS. Results indicated that patients receiving Aubagio experienced a significant relative risk reduction in the annualized relapse rate (ARR) of 31% when compared with patients receiving placebo. In addition, the time to disability progression was significantly reduced in the Augabio 14 mg

group, and patients in both Aubagio groups had significantly fewer MRI brain lesions per scan than those in the placebo group.

In a second randomized, double-blind, placebo-controlled clinical trial involving 179 patients with RMS, the mean number of unique active lesions per MRI brain scan during a 36-week treatment period was significantly lower in patients treated with Aubagio when compared with placebo.

Clinical comparisons between Aubagio and other oral agents used to treat patients with RMS are not available.

RELAPSING MULTIPLE SCLEROSIS

STUDY DESIGN	Randomized, double-blind, placebo-controlled clinical trial (n=1088).
INCLUSION CRITERIA	Patients aged 18 to 55 years with a definite diagnosis of MS and exhibiting a relapsing clinical course, with or without progression, and who experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. Subjects had not received interferon-beta for at least 4 months or any other preventive MS medications for at least 6 months before study entry, and these medications were not permitted during the study.
EXCLUSION CRITERIA	Patients with other systemic diseases, pregnant patients, or female patients who planned to conceive during the trial period were excluded.
TREATMENT REGIMEN	Patients were randomized to receive oral Aubagio 7 mg (n=366), Aubagio 14 mg (n=359), or placebo (n=363). At entry, patients had an Expanded Disability Status Scale (EDSS) score of <= 5.5. The mean age of the study population was 37.9 years, the mean disease duration was 5.33 years, and the mean EDSS at baseline was 2.68. A total of 91.4% had relapsing remitting MS (RRMS) and 8.6% had a progressive form of MS with relapses. Patients took Aubagio 14 mg for a mean of 627 days, Aubagio 7 mg for a mean of 635 days, and placebo for a mean of 631 days. Neurologic evaluations were performed at screening, every 12 weeks until week 108 and at unscheduled visits for suspected relapse. An MRI was performed at screening, and at weeks 24, 48, 72, and 108. The primary endpoint was the annualized relapse rate (ARR).
RESULTS	The ARR was significantly reduced in patients treated with either 7 mg or 14 mg of Aubagio compared with patients who received placebo. There was a consistent reduction of the ARR noted in subgroups defined by sex, age, prior MS therapy, and baseline disease activity. The time to disability progression sustained for 12 weeks, as measured by at least a 1-point increase from a baseline EDSS of <= 5.5 or a 0.5 point increase from a baseline EDSS of > 5.5, was statistically significantly reduced only in the Aubagio 14 mg group when compared with placebo. The ARR was 0.369 (p=0.0005), 0.37 (p=0.0002), and 0.539 in the Aubagio 14 mg, 7 mg, and placebo groups, respectively. The relative risk reduction was 31% in each Aubagio group. The percent of patients remaining relapse-free at week 108 was 56.5%, 53.7%, and 45.6%, respectively, in the Aubagio 14 mg, 7 mg, and placebo groups. The percent disability progression at week 108 was 20.2% (p=0.028; hazard ratio (HR), 0.7), 21.7% (p=0.084; HR, 0.76), and 27.3%, respectively, in the same treatment groups. For the MRI endpoints, the median change from baseline in total lesion volume at week 108 was 0.345 mL (p=0.0003), 0.755 mL (p=0.0317), and 1.127

	mL, respectively, in the Aubagio 14 mg, 7 mg, and placebo groups. The mean number of gadolinium-enhancing T1 lesions per scan was 0.261 ($p < 0.0001$), 0.57 ($p < 0.0001$), and 1.331 in the same groups, respectively.
SAFETY	Diarrhea, nausea, hair thinning, and abnormal liver function tests were more common with Aubagio than with placebo.

Contraindications[1]

- Severe hepatic impairment
- Pregnancy
- Current leflunomide treatment

Warnings and Precautions[1]

- WBC and platelet decreases have been reported; monitor with CBC and suspend therapy for serious infections.
- Peripheral neuropathy has been reported; discontinuation and accelerated elimination may be necessary.
- Acute renal failure and hyperkalemia have been reported; monitor renal function and potassium if symptomatic.
- Stevens-Johnson syndrome and toxic epidermal necrolysis may occur; discontinue and use accelerated elimination procedure.
- Blood pressure increases have been reported; monitor and manage as necessary.
- Hepatotoxicity may occur; increased risk expected with pre-existing liver disease; monitor and if suspected, discontinue and use accelerated elimination procedure.
- May increase risk of teratogenic effects or fetal death (animal data); exclude pregnancy prior to initiation in female of childbearing potential and confirm use of reliable contraception.
- Interstitial lung disease, new or worsening, may occur; monitor and if suspected, discontinuation and accelerated elimination may be necessary.

Adverse Effects[1]

Most common, greater than 5%

	AUBAGIO		**PLACEBO**
PRIMARY SYSTEM ORGAN CLASS	**14 mg**	**7 mg**	
Influenza	12%	9%	10%
Upper respiratory tract infection	9%	9%	7%
Bronchitis	8%	5%	6%
Sinusitis	6%	4%	4%
Headache	19%	22%	18%
Paraesthesia	10%	9%	8%
Diarrhea	18%	15%	9%
Nausea	14%	9%	7%
Abdominal pain upper	6%	5%	4%
Alopecia	13%	10%	3%
Musculoskeletal pain	4%	5%	3%

Drug Interactions[1]

- CYP1A2 substrates: alosetron, caffeine, duloxetine, theophylline, tizanidine
- CYP2C8 substrates: paclitaxel, pioglitazone, repaglinide, rosiglitazone
- Ethinyl estradiol
- Levonorgestrel
- Warfarin

Dosage and Administration[1]

Give 7 mg or 14 mg orally once daily, with or without food.

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST
Teriflunomide	Aubagio	Genzyme	7 mg tablets	1 tablet daily	$ 132.46 (WAC)*
			14 mg tablets	1 tablet daily	$ 132.46 (WAC)*
Fingolimod	Gilenya	Novartis	0.5 mg capsules	1 capsule daily	$ 179.14 (MAC)**

*Wholesale Acquisition Cost (WAC)
** Maximum Allowable Cost (MAC)

Conclusion

Aubagio is a once daily pyrimidine synthesis inhibitor that has demonstrated efficacy for the treatment of patients with RMS. MS affects about 400,000 people in the United States. There are 4 basic presentations of MS, the most common being the relapsing form. The strategies for treating MS include reducing the number of attacks, reducing the number of lesions observed on MRI scans, slowing the progression of disability, and improving the speed of recovery. Aubagio is the second oral drug that has been approved for RMS, and it has a favorable long-term safety profile. However, direct clinical comparisons between Aubagio and other oral RMS agents are not available. Several additional oral medications for RMS are currently under development.

Recommendation

This drug is being reviewed for inclusion into the state specific Preferred Drug List and is currently under solicitation.

References

1. Product Information: Aubagio®, teriflunomide tablets. Genzyme Corp., a Sanofi Company, Cambridge, MA, 09/2012.
2. Warnke C, Meyer zu Horste G, Hartung H et al: Review of teriflunomide and its potential in the treatment of multiple sclerosis. Neuropsychiatr Dis Treat 2009; 5:333-340.
3. Gold R & Wolinsky JS: Pathophysiology of multiple sclerosis and the place of teriflunomide. Acta Neurol Scand 2011; 124(2):75-84.
4. Palmer AM: Teriflunomide, an inhibitor of dihydroorotate dehydrogenase for the potential oral

treatment of multiple sclerosis. Curr Opin Investig Drugs 2010; 11(11):1313-1323.
5. Freedman MS, Wolinsky JS, Wamil B et al: Teriflunomide Multiple Sclerosis Trial Group and the MRI Analysis Center: Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial. Neurology 2012; 78(23):1877-1885.
6. Miller AE, O'Connor P, Wolinsky JS et al: Teriflunomide Multiple Sclerosis Trial Group: Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. Mult Scler 2012; 18(11):1625-1632.
7. Confavreux C, Li DK, Freedman MS et al: Teriflunomide Multiple Sclerosis Trial Group: Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. Mult Scler 2012; 18(9):1278-1289.
8. O'Connor P, Wolinsky JS, Confavreux C et al: TEMSO Trial Group: Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011; 365(14):1293-1303.
9. O'Connor PW, Li D, Freedman MS et al: Teriflunomide Multiple Sclerosis Trial Group: University of British Columbia MS/MRI Research Group: A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology 2006; 66(6):894-900.

Prepared by: Katie Wilbers, PharmD
Date: February 8, 2013

