PDL NEW DRUG REVIEW

Proprietary Name: Aubagio®
Common Name: teriflunomide
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Gilenya	Non-Preferred with Conditions

Summary

Indications and Usage: For the treatment of those with relapsing forms of multiple sclerosis (MS). This is a pregnancy category X medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Drug Interactions: It is thought that teriflunomide is an inhibitor of CYP2C8 (could increase serum levels of CYP2C8 substrates) and an inducer of CYP1A2 (thus could decrease serum levels of CYP1A2 substrates). Thus, it is recommended that patients be monitored if on concomitant drugs that are metabolized by CYP2C8 (such as repaglinide, paclitaxel, pioglitazone, and rosiglitazone) or if on concomitant drugs that are metabolized by CYP1A2 (such as duloxetine, alosetron, theophylline, and tizanidine).

There was a 25% decrease in INR when teriflunomide was given concomitantly with warfarin as compared with warfarin alone. It is thus recommended to perform thorough monitoring of INR if using concomitantly with warfarin.

An increase in ethinyl estradiol and levonorgestrel was seen when these oral contraceptives were given concomitantly with repeated doses of teriflunomide. The type or dose of oral contraception should be considered if used concomitantly with teriflunomide.

Concurrent use of teriflunomide with leflunomide is contraindicated.

Dosage Forms: Tablets: 7mg, 14mg

Recommended Dosage: Take one tablet (7mg or 14mg) once daily, with or without food. To assess safety issues, several monitoring parameters need to be implemented. Within 6 months before initiation of Aubagio®, transaminase and bilirubin levels must be obtained, as well as a complete blood count (CBC). All should be screened for latent tuberculosis infection with a tuberculin skin test prior to starting therapy. Lastly, blood pressure should be checked prior to and then periodically thereafter during treatment.

Dose adjustments are not required in those with mild or moderate hepatic impairment; however, use is contraindicated in those with severe hepatic impairment. Dose adjustment is not required for those with renal impairment.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most commonly reported adverse events with teriflunomide 14mg included influenza (2%), upper respiratory tract infection (2%), bronchitis (2%), sinusitis (2%), cystitis (3%), gastroenteritis viral (3%), oral herpes (2%), neutropenia (3.97%), seasonal allergy (2%), anxiety (2%), headache (1%), paraesthesia (2%), sciatica (2%), carpal tunnel syndrome (2.97%), blurred vision (2%), palpitations (1%), hypertension (2%), diarrhea (9%), nausea (7%), upper abdominal pain (2%), toothache (2%), alopecia (10%), acne (2%), alanine aminotransferase increased (7%), aspartate aminotransferase increased (2%), weight decreased (1%), and WBC count decreased (1%).

In placebo-controlled trials, treatment-emergent hyperkalemia (>7.0mmol/L) was reported in 1.0% of the teriflunomide group vs 0.2% of the placebo group. Two subjects in the teriflunomide group had hyperkalemia with acute renal failure. It is therefore recommended that potassium levels be checked in those with symptoms of hyperkalemia or with acute renal failure.

In placebo-controlled trials, the mean change from baseline in systolic BP was 2.9mmHg with the 7mg dose and 2.7mmHg with the 14mg dose of teriflunomide, as compared with a decrease of 1.3mmHg for the placebo group. It is therefore recommended that BP be taken before the start of therapy and periodically thereafter. If elevations of BP occur with Aubagio® use, manage the BP appropriately.

Contraindications: In those with severe hepatic impairment, in those who are pregnant or women of childbearing potential not able to use reliable contraception, and concurrent use with leflunomide.

Manufacturer: Genzyme Corporation, a Sanofi Company

Analysis: Teriflunomide is a de novo pyrimidine synthesis inhibitor of the dihydroorotate dehydrogenase (DHO-DH) enzyme. It is an immunomodulatory agent with anti-inflammatory properties. Although the exact mechanism of action in MS is not known, it is thought that it may involve a reduction in the number of activated lymphocytes in the CNS.

A boxed warning exists regarding hepatotoxicity with Aubagio® use. Severe liver injury, including fatal liver failure, has been reported with leflunomide use. It is expected that a similar risk would occur with teriflunomide use. Use of Aubagio® with other hepatotoxic drugs may increase the risk of severe liver injury. Therefore, it is recommended that transaminase and bilirubin levels be obtained within 6 months of starting therapy, and ALT levels be monitored monthly for the first six months of therapy. Furthermore, if drug induced liver injury is suspected, Aubagio® therapy should be discontinued and an accelerated elimination procedure with cholestyramine or charcoal should be started. Those with pre-existing liver disease may be at increased risk of elevated serum transaminases with Aubagio® use, and thus use is contraindicated in those with severe liver impairment.

A boxed warning also exists regarding the risk of teratogenicity, warning of the risk of major birth defects with use. Aubagio® is a pregnancy category X product and use is contraindicated in pregnant women or women of childbearing potential who are not able to use reliable contraception. Women of childbearing potential should not start therapy with Aubagio® until pregnancy is excluded and it has been confirmed that reliable contraception is being used. Once Aubagio® treatment is discontinued, it is recommended that women of childbearing potential undergo an accelerated elimination procedure, as teriflunomide is eliminated slowly and takes on average 8 months to reach plasma levels less than 0.02mg/L (and in certain individuals it could take up to 2 years).

One double-blind, placebo-controlled study (N=1088) assessed the safety and efficacy of teriflunomide 7mg and 14mg in adults with relapsing forms of MS over 108 weeks. All included in the trial had experienced at least 1 relapse in the preceding year and had not used interferon-beta for at least 4 months. The primary endpoint was the annualized relapse rate (ARR).

Results of the clinical endpoints suggested that the ARR was significantly reduced in the teriflunomide 14mg group (ARR 0.369; p=0.0005) and the 7mg group (ARR 0.370; p=0.0002) as compared with placebo (ARR 0.539). This resulted in a relative risk reduction of 31% with both the teriflunomide 7mg and 14mg dose. Furthermore, 56.5% of the 14mg group and 53.7% of the 7mg group remained relapse-free at week 108 as compared with 45.6% of the placebo group. (This translates into an NNT of 10 for the 14mg dose and an NNT of 13 for the 7mg dose.) Only 20.2% of the 14mg dose group (p=0.028) and 21.7% of the 7mg dose group (p=0.084) had disability progression at week 108 as compared with 27.3% of the placebo group.

Results of the MRI endpoints suggest that there was a 0.345 median change from baseline in total lesion volume (p=0.0003) at week 108 with the 14mg dose and 0.755 median change with the 7mg group (p=0.0317) as compared with 1.331 with placebo. Lastly, the mean number of Gd-enhancing T1-lesions per scan was 0.261 with the 14mg dose (p<0.0001) and 0.570 with the 7mg dose (p<0.0001) as compared with 1.331 with placebo.

Study 2 was a randomized, double-blind, placebo-controlled 36-week study (N=179) to assess for the efficacy of teriflunomide in adult subjects with MS with relapse. The primary outcome was the average number of unique active lesions/MRI scan during treatment. Results suggest that there was a statistically significantly lower mean number of unique active lesions per brain MRI scan with the 14mg group (0.98; p=0.0052) and the 7mg group (1.06; p=0.0234) as compared with placebo (2.69).

One randomized, double-blind, phase II study (N=118) by Freedman et al[2] included 3 treatment arms, comparing placebo plus interferon beta with teriflunomide 7mg or 14mg used adjunctively with interferon beta. The primary outcome was safety, while an efficacy assessment was also performed. Teriflunomide used adjunctively with interferon beta was found to be safe, and discontinuations due to adverse events were comparable between treatment arms. For efficacy, results suggest that there was a significantly greater reduction in the number of T1-Gd lesions per scan with both the 7mg and 14mg teriflunomide plus interferon groups as compared with the placebo and interferon group (p=0.0005 for the 7mg group and p<0.0001 for the 14mg teriflunomide group).

Aubagio® is indicated only for a specific type of multiple sclerosis and its place in therapy relative to current MS agents is not clear as there is only data from one comparative trial available. It is recommended that Aubagio® remain non-preferred and be available to those who meet the indication and have failed or are unable to tolerate currently preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☐ **Non-Preferred**
- ☒ **Non-Preferred with Conditions**

Definitions: **1. Number Needed to Treat (NNT):** The number of subjects required to bring about one response on the primary outcome.

References

[1] Aubagio [package insert]. Cambridge, MA: Genzyme Corp, A Sanofi Company; 2012.

[2] Freedman MS, Wolinsky JS, Wamil B, et al. Teriflunomide added to interferon-β in relapsing multiple sclerosis: a randomized phase II trial. *Neurology.* 2012; 78(23): 1877-85.