

## Mellen Center Approaches: Use of Teriflunomide in MS

### What is teriflunomide and how does it work?

Teriflunomide (Brand name Aubagio, Sanofi Aventis) was approved by the US FDA in September, 2012, as an oral disease modifying drug for relapsing forms of MS. Approval was based on a phase 3 study enrolling 1,088 patients, who were randomized to receive placebo, teriflunomide, 7 mg daily, or teriflunomide, 14 mg daily. This study showed that both doses of teriflunomide reduced relapse rate and MRI lesions, and the higher dose reduced disability progression. Teriflunomide is an immunomodulatory agent with anti-inflammatory properties. Teriflunomide inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is unknown but may involve a reduction in the number of activated lymphocytes in CNS. Teriflunomide is the active metabolite of leflunomide (Arava), currently marketed for treatment of Rheumatoid Arthritis.

In the study leading to marketing approval for teriflunomide, active treatment reduced the annualized relapse rate by 31%. The 14 mg dose reduced the risk of confirmed EDSS worsening by 30%, and new MRI lesions formation by about 75%. Relapse rate reduction in this trial was lower than relapse rate reduction observed with natalizumab, fingolimod, or dimethylfumarate, and similar to relapse rate reduction observed in placebo-controlled trials of interferon beta and glatiramer acetate.

### How is teriflunomide administered?

Teriflunomide is administered as a single 7 mg or 14 mg tablet, once daily, with or without food. Significant data exists demonstrating that efficacy is higher with the 14 mg dosage. This is most evident on MRI outcomes, but is also evident on relapse severity and relapse rate outcomes. We generally recommend the 14 mg dosage. For patients with

more mild MS, observation during treatment with the 7 mg dose is reasonable.

### For whom should teriflunomide be considered?

Teriflunomide was approved to treat relapsing forms of MS. It is an appropriate drug for treatment-naïve relapsing MS patients, or as an alternative drug for patients with ongoing disease activity despite treatment, intolerable side effects, or logistical issues with other MS therapies.

### Are there any restrictions on who can take teriflunomide?

Clear contraindications for teriflunomide include pregnancy, significant liver dysfunction, and concomitant use of leflunomide. Teriflunomide should be avoided in patients with chronic infection, in female patients who anticipate becoming pregnant in the foreseeable future, and in male patients who anticipate impregnating their partner.

### May teriflunomide be used as initial MS therapy?

Teriflunomide is approved as first line therapy (i.e. patients are not required to have tried other medications before teriflunomide), although long-term experience with its use is limited.

### Should patients switch from a previously-available injected medication to teriflunomide?

We anticipate many patients currently on an injectable therapy will be attracted to teriflunomide's oral route of administration. However, if a patient is stable clinically and radiographically, and he/she is not experiencing significant adverse effects, in general, we recommend not switching therapy. For JC virus antibody-positive patients on natalizumab who are concerned about the risk of progressive multifocal leukoencephalopathy, teriflunomide is a reasonable consideration.

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### **What side effects and safety issues does teriflunomide have?**

Teriflunomide is generally safe and well tolerated but there are recognized risks. Two notable risks are hepatotoxicity and 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. For this reason, we recommend checking transaminase and bilirubin levels before initiating teriflunomide, and monitoring ALT levels monthly for six months.

Based on animal data, teriflunomide may cause major birth defects if used during pregnancy. Therefore, teriflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during teriflunomide use.

In case of severe liver injury or pregnancy while using teriflunomide, drug clearance may be enhanced by oral administration of cholestyramine or activated charcoal for 11 days.

The most common side effects of teriflunomide are: increased alanine aminotransferase (ALT), alopecia, influenza symptoms, diarrhea, nausea, and paresthesias. In clinical trials, 2% of patients using teriflunomide developed peripheral neuropathy.

### **Is teriflunomide safe during pregnancy?**

Risk to the fetus is one of the main concerns with using teriflunomide for MS disease management, particularly since most relapsing MS patients are in the child-bearing years. While there are no adequate and well-controlled studies evaluating teriflunomide in pregnant women, based on animal studies, teriflunomide may increase the risk of teratogenic effects or fetal death when administered to a pregnant woman. Women or men of childbearing potential must not be started on teriflunomide until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting treatment with teriflunomide, patients must be fully counseled on the potential for serious risk to the

fetus. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing and, if positive, the physician and patient must discuss the risk to the fetus. It is possible that rapidly lowering the plasma concentration of teriflunomide by instituting an accelerated elimination procedure may decrease the risk to the fetus from teriflunomide.

### **How long should a patient wait after stopping another disease modifying therapy before starting teriflunomide?**

There is no data regarding optimal wash-out times. The theoretical increased risk of complications from incomplete wash-out from the previous therapy needs to be balanced against the risk of return of MS disease activity during a wash-out period. In some patients, the return of disease activity can be very severe. Decisions regarding wash-out are influenced by the treatments and the patients underlying disease activity. Because teriflunomide may result in reduced neutrophils, lymphocytes, and platelets, we recommend allowing sufficient time for the blood counts to normalize after discontinuing other medication that are associated with cytopenia (e.g. fingolimod, interferon beta).

### **What testing is required prior to teriflunomide therapy and how should this be monitored?**

Prior to therapy, a complete blood count (CBC), bilirubin, liver enzymes, and pregnancy test (for women) are recommended. We recommend monthly liver enzymes for 6 months, with less frequent CBC and liver enzymes thereafter.

### **Does teriflunomide need to be stopped for surgery?**

There are no reports of complications related to surgery in patients receiving teriflunomide, so we do not recommend stopping teriflunomide for surgery.

### **Does the risk of infection relate to peripheral blood white blood cell or lymphocyte counts?**

There is no clear relationship between the level of lymphocyte reduction and the incidence (or severity) of infections. Therefore, monitoring blood counts is not recommended to assess the risk of infection, but may be useful to monitor for toxicity.

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### **Is teriflunomide effective in progressive MS?**

The effectiveness and safety of teriflunomide in primary and secondary progressive MS is not known.

### **Can teriflunomide be used in combination with other MS disease therapies?**

There are no data concerning the safety or utility of combining teriflunomide with other MS disease therapies. Co-administration of teriflunomide with immunosuppressant medications would be expected to increase the risk of infection.

### **Can teriflunomide be combined with MS symptom medications?**

Teriflunomide can be combined with MS symptom medications without problem. There are no known interactions between teriflunomide and other medications.

### **Can teriflunomide be combined with medications for other conditions?**

There are no medications known to interact with teriflunomide.

### **Can the dose of teriflunomide be increased beyond 14 mg daily?**

The approved dose of teriflunomide is 14 mg daily. Higher doses have not been evaluated and are not recommended.

### **REFERENCES**

1. O'Connor, P, Wolinsky, JS, Confavreux, C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *New England Journal of Medicine*. 2011; 365:1293-1303.
2. Package Insert: NDA 202992 – FDA Approved Labeling Text dated September 12, 2012