FOR YOUR PATIENTS WITH RELAPSING FORMS OF MULTIPLE SCLEROSIS

INITIATING ORAL

TERIFLUNOMIDE (teriflunomide) THERAPY

INDICATION

MAR-TERIFLUNOMIDE (teriflunomide) is indicated as monotherapy for the treatment of patients with relapsing remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

IMPORTANT SAFETY INFORMATION

WARNING: HEPATOTOXICITY AND EMBRYOFETAL TOXICITY

• 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 teriflunomide with other potentially hepatotoxic drugs may increase the risk of severe liver injury.

• Obtain transaminase and bilirubin levels within 6 months before initiation of teriflunomide therapy. Monitor ALT levels at least monthly for 6 months after starting teriflunomide. If drug-induced liver injury is suspected, discontinue TERIFLUNOMIDE AND START AN ACCELERATED ELIMINATION PROCEDURE WITH CHOLESTYRAMINE OR ACTIVATED CHARCOAL. Teriflunomide 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 TERIFLUNOMIDE.

• Teriflunomide 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 teriflunomide in females of reproductive potential. Advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Stop teriflunomide and use an accelerated drug elimination procedure if the patient becomes pregnant.

INITIATING ORAL TERIFLUNOMIDE THERAPY

One tablet, once daily

• PrMAR-TERIFLUNOMIDE (teriflunomide) is taken orally once daily, with or without food

Monitoring liver enzymes

• Teriflunomide is contraindicated in patients with severe hepatic impairment

• Obtain transaminase and bilirubin levels within 6 months before starting teriflunomide and monitor alanine aminotransferase (ALT) levels monthly for at least 6 months after starting teriflunomide

Considerations for females of reproductive potential taking TERIFLUNOMIDE

Before starting TERIFLUNOMIDE therapy

• Teriflunomide is contraindicated in pregnant women and females of reproductive potential who are not using effective contraception. Exclude pregnancy and confirm use of effective contraception

• Counsel patients fully on the potential for serious risks to the fetus

During TERIFLUNOMIDE therapy

• Counsel patients to avoid pregnancy. If there is any reason to suspect pregnancy, patients should notify their health care professional (HCP) immediately for pregnancy testing

• If a patient becomes pregnant or wants to become pregnant during teriflunomide therapy, there is an accelerated elimination procedure that reduces plasma drug levels by >98% within 11 days. Blood levels <0.02 mcg/mL are thought to pose minimal risk to the fetus, based on animal data*

• Women who become pregnant while taking teriflunomide may enroll in the CGPA-Member Teriflunomide Enhanced Pharmacovigilance Pregnancy Active Surveillance Program . The purpose of the registry is to collect information on the safety of the therapy during pregnancy. Details about this registry is available on Marcan's website (www.marcanpharma.com)

Considerations for male patients taking TERIFLUNOMIDE

• Instruct patients and their female partners to use effective contraception to minimize any possible risk

• Teriflunomide is detected in human semen. Animal studies to specifically evaluate the risk of male-mediated fetal toxicity have not been conducted

• If patients wish to father a child, discontinue teriflunomide therapy and either administer the accelerated elimination procedure or wait until plasma concentrations of teriflunomide are <0.02 mcg/mL*

Monitoring for infection

• Obtain a complete blood count (CBC) within 6 months before starting treatment with teriflunomide and as clinically indicated. teriflunomide is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections

• Patients with active acute or chronic infections should not start treatment until the infection is resolved

• Prior to initiating teriflunomide, screen patients for latent tuberculosis infection with a tuberculin skin or blood test

Other assessments

• Check blood pressure before starting teriflunomide treatment and periodically thereafter

*Teriflunomide is eliminated slowly from the plasma. Without accelerated elimination, it takes an average of 8 months, but because of individual variations in drug clearance, it may take up to 2 years to reach plasma concentrations of <0.02 mcg/mL

Patient name: _____

Therapy start date: _____

ROUTINE MONITORING RECOMMENDED:

Before starting teriflunomide therapy:

- ☐ Complete the MAR-TERIFLUNOMIDE Prescriber's checklist
- ☐ Check transaminase and bilirubin levels (within 6 months before starting therapy)
- ☐ Exclude pregnancy and confirm use of effective contraception
- ☐ Counsel patients on the potential for serious risk to the fetus and use of effective contraception in females of reproductive potential
- ☐ Obtain a complete blood count (CBC) (within 6 months before starting therapy)
- ☐ Screen for latent tuberculosis infection
- ☐ Check baseline blood pressure

During teriflunomide therapy

- ☐ Monitor alanine aminotransferase (ALT) levels monthly (for 6 months)
- ☐ Check blood pressure periodically
- ☐ Counsel patients to continue use of effective contraception during therapy

> **Mar-teriflunomide is contraindicated in patients with severe hepatic impairment, in pregnant women, in females of reproductive potential who are not using effective contraception, in patients with a history of hypersensitivity to teriflunomide, its inactive ingredients or leflunomide, or who are currently taking leflunomide**

Reference: Mar-teriflunomide Product monograph, labeling information of reference product Aubagio.

IMPORTANT SAFETY INFORMATION

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 teriflunomide.

• 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 teriflunomide. In clinical trials, if ALT elevation was >3 times the ULN on 2 consecutive tests, patients discontinued teriflunomide and underwent accelerated elimination. Consider additional monitoring if co-administering teriflunomide 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).

• **Embryofetal Toxicity:** Teriflunomide 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. teriflunomide is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception.

Exclude pregnancy before starting teriflunomide in females of reproductive potential. Advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure (AEP) after teriflunomide treatment. If a woman becomes pregnant while taking teriflunomide, stop treatment, apprise patient of the potential risk to a fetus, and perform an AEP to achieve an teriflunomide plasma concentration of <0.02 mg/L. Upon discontinuing teriflunomide, it is recommended all females of reproductive potential undergo an AEP.

Women receiving teriflunomide who wish to become pregnant must discontinue teriflunomide and undergo an AEP, until plasma concentrations of teriflunomide are <0.02 mg/L. Men wishing to father a child should also stop teriflunomide and either undergo an AEP or wait until plasma concentration of teriflunomide is <0.02 mg/L.

Women who become pregnant while taking teriflunomide may enroll in the CGPA-Member Teriflunomide Enhanced Pharmacovigilance Pregnancy Active Surveillance Program. Details about this registry is available on Marcan's website (www.marcanpharma.com).

• **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 teriflunomide.

• **Bone Marrow Effects/Immunosuppression Potential/Infections:** Decreases in white blood cell counts, mainly of neutrophils and lymphocytes, and platelets have been reported with teriflunomide. Thrombocytopenia, including rare cases with platelet counts less than 50,000/mm3, has been reported in the post-marketing 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. Teriflunomide is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe uncontrolled infections. Tuberculosis (TB) has been observed in clinical studies of teriflunomide. 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:** Teriflunomide 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 teriflunomide. Very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms have also been reported with leflunomide. If a severe skin reaction develops with teriflunomide, 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 teriflunomide. 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 teriflunomide. 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 teriflunomide. 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 teriflunomide 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 co-administered 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 teriflunomide.