Pr MINT-TERIFLUNOMIDE

GUIDE FOR PRESCRIBERS

Teriflunomide Tablets
14 mg Teriflunomide

INDICATION

Mint-Teriflunomide is indicated for 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.

CONTRAINDICATION

Mint-Teriflunomide (teriflunomide) is contraindicated in patients:

- with known hypersensitivity to teriflunomide, leflunomide (the parent compound) or to any of the nonmedicinal ingredients in the formulation who are currently treated with leflunomide.
- Co-administration of teriflunomide with leflunomide is contraindicated
- with severe hepatic impairment.
- who are pregnant or women of childbearing potential not using reliable contraception. Mint-Teriflunomide may cause fetal harm when administered to a pregnant woman. Pregnancy must be excluded before start of treatment.
- with immunodeficiency states (e.g., AIDS)
- with impaired bone marrow function or significant anemias, leucopenia, neutropenia, or thrombocytopenia with serious active infections.

SERIOUS WARNINGS & PRECAUTIONS

Hepatotoxicity

Severe liver injury including fatal liver failure occurred rarely in the post marketing setting. Concomitant use of Mint-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 Mint-Teriflunomide therapy. Monitor ALT levels at least monthly for at least six months after starting Mint-Teriflunomide. If drug induced liver injury is suspected, discontinue Mint-Teriflunomide and start an accelerated elimination procedure with cholestyramine or charcoal. Mint-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 Mint-Teriflunomide.

Risk of Teratogenicity

Based on animal data, teriflunomide may cause major birth defects if used during pregnancy. Pregnancy must be excluded before starting Mint-Teriflunomide. Mint-Teriflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during Mint-Teriflunomide treatment or prior to the completion of an accelerated elimination procedure after Mint-Teriflunomide treatment. A Teriflunomide Enhanced Pharmacovigilance Pregnancy Active Surveillance Program has been established to collect information about the effect of Mint-Teriflunomide exposure during pregnancy. Physicians are encouraged to enroll pregnant women in the Teriflunomide Enhanced Pharmacovigilance Pregnancy Active Surveillance Program, or pregnant women may enroll themselves in the Teriflunomide Enhanced Pregnancy Surveillance Program by calling Mint Pharmaceuticals. at 1-877-398-9696 or by emailing drugsafety@mintpharma.com.

WARNINGS & PRECAUTIONS

Accelerated Elimination Procedure

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mg/L, however, due to individual variations in drug clearance it may take as long as 2 years. An accelerated elimination procedure could be used at any time after discontinuation of Mint-Teriflunomide.

Elimination can be accelerated by either of the following procedures:

- Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days.

If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly.

At the end of 11 days, both regimens successfully accelerated teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations. Use of the accelerated elimination procedure may potentially result in a gradual return of disease activity if the patient had been responding to Mint-Teriflunomide treatment.

Cardiovascular

Hypertension was reported as an adverse reaction in 4.2% of patients treated with 14 mg of teriflunomide, compared with 2% on placebo for up to 2 years in the placebo controlled trials.

Check blood pressure before the initiation of treatment with Mint-Teriflunomide and periodically throughout treatment. Elevated blood pressure should be appropriately managed during treatment with Mint-Teriflunomide.

Hematologic

A mean decrease in white blood cell (WBC) count of approximately 15% (mainly neutrophils and lymphocytes) and in platelet count of approximately 10% was observed in placebo-controlled trials with teriflunomide as compared to baseline.

Rare cases of pancytopenia, agranulocytosis and thrombocytopenia have been reported in the post-marketing setting with leflunomide. A similar risk is expected for teriflunomide. Obtain a complete blood cell count (CBC) within 6 months before initiating treatment with Mint-Teriflunomide and periodically during treatment. Further monitoring should be based on signs and symptoms suggestive of infection.

Switching therapies

In any situation in which the decision is made to switch to or from Mint-Teriflunomide, from or to another agent with a known potential for hematologic suppression, monitoring for hematologic toxicity is recommended, because there will be overlap of systemic exposure to both compounds, due to the slow elimination from plasma of Mint-Teriflunomide and some of the other therapies (e.g., natalizumab, fingolimod). Use of an accelerated elimination procedure may decrease this risk when switching to another therapy but may also potentially result in return of disease activity if the patient had been responding to Mint-Teriflunomide treatment.

In patients with pre-existing anemia, leucopenia, and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of hematological disorders is increased. If such effects occur, the accelerated elimination procedure should be considered.

Hepatic/Biliary/Pancreatic

Hepatic:

Liver function abnormalities have been reported in some patients treated with teriflunomide in clinical trials. Severe liver injury including fatal liver failure occurred rarely in the post marketing setting. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking Mint-Teriflunomide. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) greater than two times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with Mint- Teriflunomide. Mint-Teriflunomide is contraindicated in patients with severe hepatic impairment.

Elevations of liver enzymes have been observed in patients receiving teriflunomide. Cases of drug-induced liver injury (DILI) have been observed in the post-marketing setting, sometimes life-threatening. Due to the potential for severe liver injury, exercise caution and closely monitor patients if other known or potentially hepatotoxic drugs are used in combination with Mint-Teriflunomide or if there is a history of drug-induced hepatotoxicity. For all patients, obtain serum transaminase and bilirubin levels within 6 months before initiating treatment with Mint-Teriflunomide. Monitor ALT levels at least monthly for at least six months after starting Mint-Teriflunomide. Additional monitoring is recommended if Mint-Teriflunomide is used with other potentially hepatotoxic drugs or if there is a history of drug induced hepatotoxicity. Consider discontinuing Mint-Teriflunomide if serum transaminase increase (greater than three times the ULN) is confirmed.

Monitor serum transaminase and bilirubin on Mint-Teriflunomide therapy, particularly in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Patients should be advised to immediately report signs or symptoms of hepatotoxicity.

If liver injury is suspected to be teriflunomide-induced, discontinue Mint-Teriflunomide and start an accelerated elimination procedure and monitor liver tests weekly until normalized. If teriflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of teriflunomide therapy may be considered.

Due to a potential for additive hepatotoxic effects, alcohol consumption should be avoided during treatment with Mint-Teriflunomide.

Hepatic Impairment:

Mint-Teriflunomide is contraindicated in patients with severe hepatic impairment. Mild and moderate hepatic impairment had no impact on the pharmacokinetics of teriflunomide. No dosage adjustment is anticipated for patients with mild and moderate hepatic impairment.

Pancreatitis:

Very rare cases of acute symptomatic pancreatitis with no alternative etiologies, have been reported during treatment with teriflunomide in MS. For patients with symptoms of acute pancreatitis that are suspected to be teriflunomide-induced, discontinue Mint-Teriflunomide and start an accelerated elimination procedure.

Immune Infections

Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved. If a patient develops a serious infection during treatment, consider suspending treatment with Mint-Teriflunomide and using an accelerated elimination procedure. Reassess the benefits and risks prior to resumption of therapy. Instruct patients receiving Mint-Teriflunomide to report symptoms of infections to a physician.

Mint-Teriflunomide is contraindicated in patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections. Medications like teriflunomide that have immunomodulatory potential may cause patients to be more susceptible to infections, including opportunistic infections.

Neurologic

Peripheral Neuropathy:

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), was reported more frequently in patients taking teriflunomide than in patients taking placebo. If a patient taking Mint-Teriflunomide develops symptoms consistent with peripheral neuropathy, such as bilateral numbness or tingling of hands or feet, consider discontinuing Mint-Teriflunomide therapy and performing an accelerated elimination procedure.

Vaccination

Vaccination with live vaccines is, however, not recommended. The long half-life of Mint-Teriflunomide should be considered when contemplating administration of a live vaccine after stopping Mint-Teriflunomide.

Renal

Severe renal impairment had no impact on the pharmacokinetics of teriflunomide. No dosage adjustment is necessary for patients with severe renal impairment. Patients with severe renal impairment undergoing dialysis were not evaluated. Teriflunomide is not recommended in this population.

Use in Women of Childbearing Potential

Mint-Teriflunomide is contraindicated in women who are pregnant or women of child-bearing potential not using reliable contraception. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. If pregnancy does occur during treatment, the drug should be immediately discontinued, and an accelerated elimination procedure should be initiated. Under these conditions, the patient should be referred to an obstetrician/gynecologist, preferably experienced in reproductive toxicity, for further evaluation and counseling. Women of childbearing potential must not be started on Mint-Teriflunomide until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting treatment with Mint-Teriflunomide, patients must be fully counseled on the potential for serious risk to the fetus. Upon discontinuing Mint-Teriflunomide, it is recommended that all women of childbearing potential not using reliable contraception undergo an accelerated elimination procedure.

Women receiving Mint-Teriflunomide treatment who wish to become pregnant must discontinue Mint-Teriflunomide and undergo an accelerated elimination procedure.

Use in males

Teriflunomide is detected in human semen. To minimize any possible risk, men not wishing to father a child and their female partners should use reliable contraception. Men wishing to father a child should discontinue use of Mint-Teriflunomide and undergo an accelerated elimination procedure.

Respiratory

Interstitial lung disease (ILD), including acute interstitial pneumonitis, has been reported with teriflunomide in the post-marketing setting. ILD and worsening of interstitial lung disease have been reported during treatment with leflunomide, the parent compound of teriflunomide. ILD is a potentially fatal disorder and may occur acutely at any time during treatment with a variable clinical presentation. The risk is increased in patients with a history of ILD.

New onset or worsening of pulmonary symptoms, such as persistent cough and dyspnea, with or without associated fever, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. If discontinuation of the drug is necessary, consider initiation of an accelerated elimination procedure.

Skin

Severe cutaneous adverse reactions (SCARs):

Cases of serious skin reactions, sometimes fatal, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in the post marketing setting in patients treated with teriflunomide for MS. If skin and/or mucosal reactions (ulcerative stomatitis) are observed which raise the suspicion of severe generalized major skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms), Mint-Teriflunomide must be discontinued, and an accelerated elimination procedure initiated immediately. In such cases patients should not be re-exposed to Mint-Teriflunomide.

New onset of psoriasis (including pustular psoriasis) and worsening of pre-existing psoriasis have been reported during use of teriflunomide. Discontinuation of treatment and initiation of an accelerated elimination procedure may be considered, taking into account the patient's disease and medical history.

SUMMARY OF IMPORTANT PRECAUTIONS TO BE TAKEN PRIOR TO INITIATING AND DURING TREATMENT WITH MINT-TERIFLUNOMIDE

Monitoring recommended prior to initiating and during treatment
(Also see Counselling Checklist):

- Obtain transaminase and bilirubin levels within 6 months before initiation of Mint-Teriflunomide therapy. Monitor ALT levels at least monthly for at least six months after starting Mint-Teriflunomide.
- Obtain a complete blood cell count (CBC) within 6 months before the initiation of treatment with Mint-Teriflunomide and periodically during treatment.
- Prior to initiating Mint-Teriflunomide, screen patients for latent tuberculosis infection.
- Check blood pressure before start of Mint-Teriflunomide treatment and periodically throughout treatment.
- Obtain a negative pregnancy test before initiation of treatment with Mint-Teriflunomide.

Testing and Counselling Checklist for physicians
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The prescriber is responsible for counseling the patient.
At first prescription, the prescriber/healthcare professional (HCP) should discuss with the patient the risks described below and provide the Patient Card.

Checklist for all patients

Patient's Name:	**Patient's age:**
First Visit date:	**Patient's sex (as assigned at birth) : Male ☐ Female ☐** **Intersex (of childbearing potential) ☐** **Intersex (not of childbearing potential) ☐**
First prescription date:	**Today's date:**

	The patient has been informed about and understands the benefits and risks associated with this treatment.
	Liver Function Elevations of liver enzymes have been observed in patients receiving teriflunomide. Discuss the risk of liver effects, and the need to conduct liver function tests before treatment and periodically during treatment.
	Educate the patient about signs and symptoms of liver disease, and about the need to contact their doctor/HCP if these develop.
	Obtain transaminase and bilirubin levels: • At least 6 months before initiation of therapy and monitor ALT levels at least monthly for at least 6 months after starting Mint-Teriflunomide. • Additional monitoring is recommended if Mint-Teriflunomide is used with other potentially hepatotoxic drugs or if there is a history of drug induced hepatotoxicity.
	Monitor serum transaminase and bilirubin in patients who develop symptoms of liver injury, such as unexplained vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine.
	If liver injury is suspected to be teriflunomide-induced, discontinue Mint-Teriflunomide and start an accelerated elimination procedure.
	Due to a potential for additive hepatotoxic effects, alcohol consumption should be avoided during treatment with Mint-Teriflunomide.
	Pregnancy If used during pregnancy, Mint-Teriflunomide may cause major birth defects and even death to babies. Pregnancy must be avoided by using effective birth control when a man or woman is on Mint-Teriflunomide. Female patients have been counselled on pregnancy, advised of the need for reliable contraception, informed about the option of the Mint-Teriflunomide accelerated elimination procedure and the Teriflunomide Enhanced Pharmacovigilance Pregnancy Active Surveillance Program.
	A negative pregnancy test result must be confirmed prior to starting treatment
	Instruct women of childbearing potential that they must use effective contraception during treatment and for two years following treatment discontinuation.

	Remind women that while on treatment, they must not become pregnant. If a woman becomes pregnant while on treatment, Mint-Teriflunomide should be immediately discontinued, and an accelerated elimination procedure should be initiated. • Medical advice should be given regarding the risk of harmful effects to the fetus associated with Mint-Teriflunomide treatment.
	Use in Males: If male patient is with a partner who can get pregnant, remind men that they must use effective contraception during treatment and for two years following treatment discontinuation. • If men wish to father a child or donate sperm, they will need to talk to their doctor about stopping treatment.
	Haematological Effects Discuss the risk of decreased blood cell counts (affecting mainly white blood cells). Discuss the need for full blood counts before treatment and during treatment, and when signs and symptoms show/present.
	Obtain a complete blood cell count (CBC) within 6 months before the initiation of treatment with Mint-Teriflunomide and periodically during treatment. • Further monitoring should be based on signs and symptoms of infection.
	Hypertension Discuss the risk of blood pressure increase. Educate the patient to tell their doctor or healthcare professional if they have hypertension, and for all patients discuss the need for blood pressure checks and appropriate management, prior to the first dose of Mint-Teriflunomide and periodically during treatment.
	Infections/Serious Infections Medications like teriflunomide that have immunomodulatory potential may cause patients to be more susceptible to infections, including opportunistic infections. Discuss risk of infections/serious infections, including the need to contact their doctor or healthcare professional in case of signs or symptoms of infection, or if the patient takes other medicines that affect the immune system. • Instruct patients receiving Mint-Teriflunomide to report symptoms of infections to a physician. • If serious infection occurs, an accelerated elimination procedure may be considered. • Prior to initiating Mint-Teriflunomide, screen patients for latent tuberculosis infection.
	Vaccines Counsel patients on vaccination and instruct them to NOT receive a “live attenuated vaccine” during treatment with Mint-Teriflunomide. • Remind them to reach out to their doctor before receiving any vaccinations during or after treatment.
	Adverse Events At prescription renewal, adverse events are checked, ongoing risks and their prevention are discussed, and checks are made to ensure adequate monitoring is taking place.
PATIENT CARD	
	Provide the patient and/or their parent/caregiver with a patient card, including filling in their contact details, and replace it when necessary.
	Discuss the content regularly during each consultation and at least annually during treatment. Provide replacement cards as necessary.
	Educate the patient and/or their parent/caregiver to show this card to any doctor or healthcare professional involved in medical care (e.g., in case of an emergency)
	Remind the patient to contact their MS doctor and/or General Practitioner if they experience any of the signs and symptoms discussed in the patient education card, including liver problems and infections.
	The patient acknowledges the importance of compliance with all the conditions of use.

By signing below, I confirm that the above-named patient is clinically cleared for treatment.

Physician Name: _____ Signature: _____ Date: _____

Medical Information & Reporting Instructions

For healthcare professionals with specific questions about Mint-Teriflunomide, please contact us at:

Mint Pharmaceuticals
6575 Davand Dr
Mississauga, Ontario
Canada
L5T 2M3
Call: toll free at 1-877-398-9696
Email: drugsafety@mintpharma.com

You can report any suspected adverse reactions associated with the use of Mint-Teriflunomide to:

- **Mint Pharmaceuticals** at 1-877-398-9696

- **Health Canada** by:
  - Visiting the Web page on Adverse Reaction Reporting (Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
  - Calling toll-free at 1 866 234-2345

- Any suspected embryo-fetal exposure to Mint-Teriflunomide must be reported immediately by telephone to Mint Pharmaceuticals. at 1-877-398-9696 or by email to drugsafety@mintpharma.com

Please consult the product monograph for important information about adverse reactions, drug interactions, and dosing and titration information, which are not discussed here. The Mint-Teriflunomide product monograph is also available by calling Mint Pharmaceuticals at 1-877-398-9696 or by visiting mint-teriflunomide.com.