HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TECFIDERA safely and effectively. See full prescribing information for TECFIDERA.

TECFIDERA® (dimethyl fumarate) delayed-release capsules, for oral use
Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Warnings and Precautions, Lymphopenia (5.4) 02/2023

INDICATIONS AND USAGE

TECFIDERA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)

DOSAGE AND ADMINISTRATION

- Starting dose: 120 mg twice a day, orally, for 7 days (2.1)
- Maintenance dose after 7 days: 240 mg twice a day, orally (2.1)
- Swallow TECFIDERA capsules whole and intact. Do not crush, chew, or sprinkle capsule contents on food (2.1)
- Take TECFIDERA with or without food (2.1)

DOSAGE FORMS AND STRENGTHS

Delayed-release capsules: 120 mg and 240 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and angioedema: Discontinue and do not restart TECFIDERA if these occur. (5.1)
- Progressive multifocal leukoencephalopathy (PML): Withhold TECFIDERA at the first sign or symptom suggestive of PML. (5.2)
- Herpes zoster and other serious opportunistic infections: Consider withholding TECFIDERA in cases of serious infection until the infection has resolved. (5.3)
- Lymphopenia: Obtain a CBC including lymphocyte count before initiating TECFIDERA, after 6 months, and every 6 to 12 months thereafter. Consider interruption of TECFIDERA if lymphocyte counts $<0.5 \times 10^9$/L persist for more than 6 months. (5.4)
- Liver injury: Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiating TECFIDERA and during treatment, as clinically indicated. Discontinue TECFIDERA if clinically significant liver injury induced by TECFIDERA is suspected. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10% and ≥2% placebo) were flushing, abdominal pain, diarrhea, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 2/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TECFIDERA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The starting dose for TECFIDERA is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally. Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dose of 240 mg twice a day should be resumed. Discontinuation of TECFIDERA should be considered for patients unable to tolerate return to the maintenance dose. The incidence of flushing may be reduced by administration of TECFIDERA with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing *[see Clinical Pharmacology (12.3)]*.

TECFIDERA should be swallowed whole and intact. TECFIDERA should not be crushed or chewed, and the capsule contents should not be sprinkled on food. TECFIDERA can be taken with or without food.

2.2 Blood Tests Prior to Initiation of Therapy

Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy *[see Warnings and Precautions (5.4)]*.

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with TECFIDERA *[see Warnings and Precautions (5.5)]*.

3 DOSAGE FORMS AND STRENGTHS

TECFIDERA is available as hard gelatin delayed-release capsules containing 120 mg or 240 mg of dimethyl fumarate. The 120 mg capsules have a green cap and white body, printed with “BG-12 120 mg” in black ink on the body. The 240 mg capsules have a green cap and a green body, printed with “BG-12 240 mg” in black ink on the body.

4 CONTRAINDICATIONS

TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or to any of the excipients of TECFIDERA. Reactions have included anaphylaxis and angioedema *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Angioedema

TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms have included difficulty breathing, urticaria, and swelling of the throat and tongue. Patients should be instructed to discontinue TECFIDERA and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema.

5.2 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has occurred in patients with MS treated with TECFIDERA. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. A fatal case of PML occurred in a patient who received TECFIDERA for 4 years while enrolled in a clinical trial. During the clinical trial, the patient experienced prolonged lymphopenia (lymphocyte counts predominantly $<0.5 \times 10^9$/L for 3.5 years) while taking TECFIDERA *[see Warnings and Precautions (5.4)]*. The patient had no other identified systemic medical conditions resulting in compromised immune system function and had not previously been treated with natalizumab, which has a known association with PML. The patient was also not taking any immunosuppressive or immunomodulatory medications concomitantly.

PML has also occurred in the postmarketing setting in the presence of lymphopenia ($<0.9 \times 10^9$/L). While the role of lymphopenia in these cases is uncertain, the PML cases have occurred predominantly in patients with lymphocyte counts $<0.8 \times 10^9$/L persisting for more than 6 months.

At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

MRI findings may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with other MS medications associated with PML. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Lower PML-related mortality and morbidity have been reported following discontinuation of another MS medication associated with PML in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

5.3 Herpes Zoster and Other Serious Opportunistic Infections

Serious cases of herpes zoster have occurred with TECFIDERA, including disseminated herpes zoster, herpes zoster ophthalmicus, herpes zoster meningoencephalitis, and herpes zoster meningomyelitis. These events may occur at any time during treatment. Monitor patients on TECFIDERA for signs and symptoms of herpes zoster. If herpes zoster occurs, appropriate treatment for herpes zoster should be administered.

Other serious opportunistic infections have occurred with TECFIDERA, including cases of serious viral (herpes simplex virus, West Nile virus, cytomegalovirus), fungal (Candida and Aspergillus), and bacterial (Nocardia, Listeria monocytogenes, Mycobacterium tuberculosis) infections. These infections have been reported in patients with reduced absolute lymphocyte counts (ALC) as well as in patients with normal ALC. These infections have affected the brain, meninges, spinal cord, gastrointestinal tract, lungs, skin, eye, and ear. Patients with symptoms and signs consistent with any of these infections should undergo prompt diagnostic evaluation and receive appropriate treatment.

Consider withholding TECFIDERA treatment in patients with herpes zoster or other serious infections until the infection has resolved *[see Adverse Reactions (6.2)]*.

5.4 Lymphopenia

TECFIDERA may decrease lymphocyte counts. In the MS placebo-controlled trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with TECFIDERA and then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but did not return to baseline. Six percent (6%) of TECFIDERA patients and <1% of placebo patients experienced lymphocyte counts $<0.5 \times 10^9$/L (lower limit of normal 0.91×10^9/L). The incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with TECFIDERA or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8 \times 10^9$/L or $\leq 0.5 \times 10^9$/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly $<0.5 \times 10^9$/L for 3.5 years) *[see Warnings and Precautions (5.2)]*.

In controlled and uncontrolled clinical trials, 2% of patients experienced prolonged, severe lymphopenia, (defined as lymphocyte counts $<0.5 \times 10^9$/L for at least six months); in this group of patients, the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy. In these patients with prolonged, severe lymphopenia, the median time for lymphocyte counts to return to normal after discontinuing TECFIDERA was 96.0 weeks.

In these controlled and uncontrolled clinical studies, among patients who did not experience prolonged, severe lymphopenia during treatment, the median times for lymphocyte counts to return to normal after discontinuing TECFIDERA were as follows:

- 4.3 weeks in patients with mild lymphopenia (lymphocyte count $\geq 0.8 \times 10^9$/L) at discontinuation,
- 10.0 weeks in patients with moderate lymphopenia (lymphocyte count 0.5 to $<0.8 \times 10^9$/L) at discontinuation, and
- 16.7 weeks in patients with severe lymphopenia (lymphocyte count $<0.5 \times 10^9$/L) at discontinuation.

TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts

Obtain a CBC, including lymphocyte count, before initiating treatment with TECFIDERA, 6 months after starting treatment, and then every 6 to 12 months thereafter, and as clinically indicated. Consider interruption of TECFIDERA in patients with lymphocyte counts less than 0.5 x 10^9/L persisting for more than six months. Given the potential for delayed recovery of lymphocyte counts, continue to obtain lymphocyte counts until their recovery if TECFIDERA is discontinued or interrupted due to lymphopenia. Consider withholding treatment from patients with serious infections until resolution. Decisions about whether or not to restart TECFIDERA should be individualized based on clinical circumstances.

5.5 Liver Injury

Clinically significant cases of liver injury have been reported in patients treated with TECFIDERA in the postmarketing setting. The onset has ranged from a few days to several months after initiation of treatment with TECFIDERA. Signs and symptoms of liver injury, including elevation of serum aminotransferases to greater than 5-fold the upper limit of normal and elevation of total bilirubin to greater than 2-fold the upper limit of normal have been observed. These abnormalities resolved upon treatment discontinuation. Some cases required hospitalization. None of the reported cases resulted in liver failure, liver transplant, or death. However, the combination of new serum aminotransferase elevations with increased levels of bilirubin caused by drug-induced hepatocellular injury is an important predictor of serious liver injury that may lead to acute liver failure, liver transplant, or death in some patients.

Elevations of hepatic transaminases (most no greater than 3 times the upper limit of normal) were observed during controlled trials *[see Adverse Reactions (6.1)]*.

Obtain serum aminotransferase, alkaline phosphatase (ALP), and total bilirubin levels prior to treatment with TECFIDERA and during treatment, as clinically indicated. Discontinue TECFIDERA if clinically significant liver injury induced by TECFIDERA is suspected.

5.6 Flushing

TECFIDERA may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). In clinical trials, 40% of TECFIDERA treated patients experienced flushing. Flushing symptoms generally began soon after initiating TECFIDERA and usually improved or resolved over time. In the majority of patients who experienced flushing, it was mild or moderate in severity. Three percent (3%) of patients discontinued TECFIDERA for flushing and <1% had serious flushing symptoms that were not life-threatening but led to hospitalization. Administration of TECFIDERA with food may reduce the incidence of flushing. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing *[see Dosing and Administration (2.1) and Clinical Pharmacology (12.3)]*.

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