EXPAND

Important Safety Information

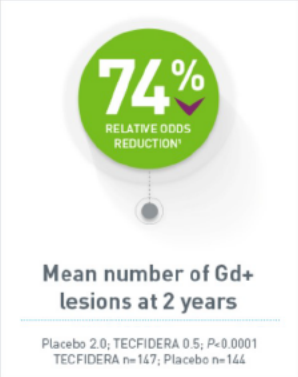
TECFIDERA Warnings and Precautions include: Anaphylaxis and Angioedema, Progressive Multifocal Leukoencephalopathy, Lymphopenia, Liver Injury, and Flushing.

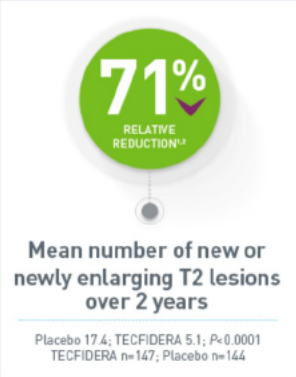
Tecfidera (dimethyl fumarate) delayed-release capsules 240 mg

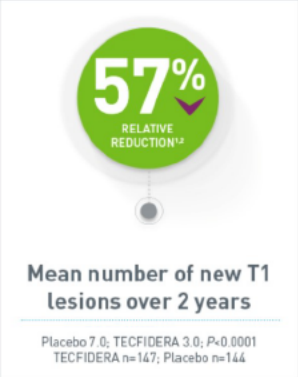
CONFIRM* Trial Efficacy

SIGNIFICANTLY REDUCED RISK AND FREQUENCY OF RELAPSES[1]

SIGNIFICANTLY REDUCED ALL MEASURES OF MRI ACTIVITY[1]







DELAYED DISABILITY PROGRESSION[1]

The reduction in the proportion with disability progression was not statistically significant[1]

Placebo 17%; TECFIDERA 13%; *P*=0.25
TECFIDERA n=359; Placebo n=363

Defining Disability Progression: At least a 1-point increase from baseline EDSS of ≥1.0, OR at least a 1.5-point increase for patients with baseline EDSS of 0 sustained for 12 weeks.[1]

see the safety profile of TECFIDERA >

Indication

Tecfidera® (dimethyl fumarate) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

Important Safety Information

TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Patients experiencing signs and symptoms of anaphylaxis and angioedema (which have included difficulty breathing, urticaria, and swelling of the throat and tongue) should discontinue TECFIDERA and seek immediate medical care.

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 in a clinical trial. PML has also occurred in the postmarketing setting in the presence of lymphopenia ($<0.8x10^9$/L) persisting for more than 6 months. While the role of lymphopenia in these cases is uncertain, the majority of cases occurred in patients with lymphocyte counts $<0.5x10^9$/L. The 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. At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms.

TECFIDERA may decrease lymphocyte counts; in clinical trials there was a mean decrease of ~30% in lymphocyte counts during the first year which then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but not to baseline. Six percent of TECFIDERA patients and <1% of placebo patients had lymphocyte counts $<0.5x10^9$/L. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8x10^9$/L or $\leq 0.5x10^9$/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly $<0.5x10^9$/L for 3.5 years). In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts $<0.5x10^9$/L for at least six months. In these patients, the majority of lymphocyte counts remained $<0.5x10^9$/L with continued therapy. A complete blood count including lymphocyte count should be obtained before initiating treatment, 6 months after starting, every 6 to 12 months thereafter and as clinically indicated. Consider treatment interruption if lymphocyte counts $<0.5x10^9$/L persist for more than six months and follow lymphocyte counts until lymphopenia is resolved. Consider withholding treatment in patients with serious infections until resolved. Decisions about whether or not to restart TECFIDERA should be based on clinical circumstances.

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. 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

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.

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.

TECFIDERA may cause flushing (e.g. warmth, redness, itching, and/or burning sensation). 40% of patients taking TECFIDERA reported flushing, which was mostly mild to moderate in severity. Three percent of patients discontinued TECFIDERA for flushing and <1% had serious flushing events that led to hospitalization. Taking TECFIDERA with food may reduce flushing. Alternatively, administration of non-enteric coated aspirin prior to dosing may reduce the incidence or severity of flushing.

TECFIDERA may cause gastrointestinal (GI) events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). Four percent of TECFIDERA patients and <1% of placebo patients discontinued due to GI events. The incidence of serious GI events was 1%. The most common adverse reactions associated with TECFIDERA versus placebo are flushing (40% vs 6%) and GI events: abdominal pain (18% vs 10%), diarrhea (14% vs 11%), nausea (12% vs 9%).

A transient increase in mean eosinophil counts was seen during the first two months.

TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage patients who become pregnant while taking TECFIDERA to enroll in the TECFIDERA pregnancy registry by calling 1-866-810-1462 or visiting www.TECFIDERApregnancyregistry.com.

Please see full Prescribing Information and Patient Information for additional Important Safety Information.

*Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.[2]
†Relapses were defined as new or recurrent neurologic symptoms not associated wi h fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.[2]

References: 1. TECFIDERA Prescribing Information, Biogen, Cambridge, MA. **2.** Fox RJ, Miller DH, Phillips JT, et al. *N Engl J Med.* 2012;367:1087-1097. Erratum in: *N Engl J Med.* 2012;367:1673. **3.** Gold R, Kappos L, Arnold DL, et al. *N Engl J Med.* 2012;367:1098-1107. Erratum in: *N Engl J Med.* 2012;367:2362.