

### **FDA Drug Safety Communication: FDA warns about case of rare brain infection PML with MS drug Tecfidera (dimethyl fumarate)**

#### **Safety Announcement**

**[11-25-2014]** The U.S. Food and Drug Administration (FDA) is warning that a patient with multiple sclerosis (MS) who was being treated with Tecfidera (dimethyl fumarate) developed a rare and serious brain infection called PML and later died. As a result, information describing this case of PML, or progressive multifocal leukoencephalopathy, is being added to the Tecfidera drug label. Patients taking Tecfidera should contact their health care professionals right away if they experience symptoms that concern them, such as new or worsening weakness; trouble using their arms or legs; or changes to thinking, eyesight, strength or balance. Health care professionals should stop Tecfidera if PML is suspected.

Tecfidera has been shown to benefit patients with relapsing forms of MS. This type of MS causes attacks or relapses – periods of time when symptoms get distinctly worse.

The patient who died was not taking any other drugs that affect the immune system or drugs that are thought to be associated with PML. This is the only confirmed case of this rare and serious brain infection reported in patients taking Tecfidera.

PML is a rare and serious brain infection caused by the John Cunningham (JC) virus. The JC virus is a common virus that is harmless in most people but can cause PML in some patients who have weakened immune systems. Symptoms of PML are diverse and may include progressive weakness on one side of the body, clumsiness, vision problems, confusion, and changes in thinking, personality, memory, and orientation. The progression of deficits can lead to severe disability or death.

The drug manufacturer, Biogen Idec, notified FDA when the MS patient died after developing PML. The patient had taken Tecfidera for more than four years. Prior to developing PML, the patient had a very low number of lymphocytes, a type of white blood cell, in her blood. Reduced lymphocyte counts can weaken the immune system, which increases the risk for PML. It is unknown whether the low lymphocyte count contributed to the development of PML in this patient, or if low lymphocyte counts are a risk factor for PML development in Tecfidera-treated patients.

We urge health care professionals and patients to report side effects involving Tecfidera to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

## **Facts about Tecfidera (dimethyl fumarate)**

- Tecfidera is a drug used to treat relapsing forms of multiple sclerosis (MS), a brain and spinal cord disease in which patients experience multiple episodes of weakness, numbness, and other nervous system signs and symptoms that partially or completely resolve over weeks or months. Patients may develop persistent symptoms and disability over time.
- Approximately 4,000 patients have taken Tecfidera in MS clinical trials, including 1,000 patients treated for at least 4 years. Biogen reports that more than 100,000 patients with MS worldwide have taken Tecfidera since FDA approved it in 2013.

## **Additional Information for Patients**

- A patient with multiple sclerosis (MS) who was being treated with Tecfidera (dimethyl fumarate) developed a rare and serious brain infection called progressive multifocal leukoencephalopathy (PML) and later died. Contact your health care professional immediately if you develop symptoms that concern you, particularly any new or worsening weakness; trouble using your arms or legs; or any changes in your thinking, eyesight, strength, or balance.
- Do not stop taking Tecfidera without first talking to your healthcare professional.
- Discuss any questions or concerns about Tecfidera and the risk of PML with your healthcare professional.
- Report any side effects of Tecfidera to your healthcare professional and to the FDA MedWatch program (see the “Contact FDA” box at the bottom of the page).

## **Additional Information for Health Care Professionals**

- Tell patients taking Tecfidera to contact you if they develop any symptoms that may be suggestive of progressive multifocal leukoencephalopathy (PML). Symptoms of PML are diverse, progress over days to weeks, and include the following: 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. The progression of deficits can lead to severe disability or death.
- Stop Tecfidera immediately at the first sign or symptom suggestive of PML and perform an appropriate diagnostic evaluation.
- Monitor lymphocyte counts in Tecfidera-treated patients according to approved labeling.
- Report adverse reactions involving Tecfidera to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

## **Data Summary**

A 54-year-old patient with multiple sclerosis (MS) being treated with Tecfidera (dimethyl fumarate) in a clinical trial died after developing progressive multifocal leukoencephalopathy (PML). The patient, who had an 18 year history of MS, had no known medical conditions that would predispose her to the development of PML. She had no history of prior use of immunosuppressive medications or Tysabri, and was not taking any concomitant immunosuppressive or immunomodulatory medications. She had

taken Copaxone (glatiramer acetate) for 3 years prior to being enrolled in a Tecfidera clinical trial. In the clinical trial, she had received placebo for two years followed by Tecfidera for approximately 4.5 years prior to developing PML. During Tecfidera treatment, she had severe lymphopenia, with lymphocyte counts consistently below 500 cells per microliter for 3.5 years before developing PML.

Two months prior to her death, the patient was hospitalized with a presumed MS relapse and treated with corticosteroids. Her condition continued to worsen, and Tecfidera was stopped at that time. A diagnostic evaluation suggested PML, and this diagnosis was confirmed when tests identified John Cunningham (JC) viral DNA in the cerebrospinal fluid. The patient developed aspiration pneumonia due to dysphagia and died approximately seven weeks after discontinuation of Tecfidera.

In March 2013, FDA approved Tecfidera for the treatment of patients with relapsing forms of MS. Tecfidera can cause low lymphocyte counts. In MS placebo-controlled trials, mean lymphocyte counts decreased by approximately 30%. Six percent (6%) of Tecfidera-treated patients experienced lymphocyte counts less than 500 per microliter (lower limit of normal is 910 per microliter).

At the time of approval, there were no known opportunistic infections, including PML, in the Tecfidera-treated patients in the clinical trial database submitted to FDA.

PML has previously been reported in Europe in patients treated with other drugs containing dimethyl fumarate. The FDA was aware of four PML cases at the time of Tecfidera approval. Three cases occurred in patients with psoriasis who took Fumaderm, a combination product sold in Germany that includes dimethyl fumarate and three different salts of monomethyl fumarate, and one case in a patient treated with a compounded product that included dimethyl fumarate. In two of these cases, the patients had previous exposure to immunosuppressive therapy. In the other two cases, patients had prolonged lymphopenia with documented lymphocyte counts below 500 cells per microliter. The contribution of dimethyl fumarate to the development of PML in these cases is unknown.