

**FDA Drug Safety Communication: FDA warns about cases of rare brain infection with MS drug Gilenya (fingolimod) in two patients with no prior exposure to immunosuppressant drugs**

**Safety Announcement**

**[08-04-2015]** The U.S. Food and Drug Administration is warning that a case of definite progressive multifocal leukoencephalopathy (PML) and a case of probable PML have been reported in patients taking Gilenya (fingolimod) for multiple sclerosis (MS). These are the first cases of PML reported in patients taking Gilenya who had not been previously treated with an immunosuppressant drug for MS or any other medical condition. As a result, information about these recent cases is being added to the drug label.

Patients taking Gilenya should contact their health care professionals right away if they experience symptoms such as new or worsening weakness; increased trouble using their arms or legs; or changes in thinking, eyesight, strength, or balance. Patients should not stop taking Gilenya without first discussing it with their health care professionals. Health care professionals should stop Gilenya and perform a diagnostic evaluation if PML is suspected.

Gilenya is an immunomodulator shown to benefit patients with relapsing forms of MS. This type of MS causes attacks or relapses, which are periods of time when symptoms get worse. Immunomodulators alter the immune system to reduce inflammation.

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, including those taking immunosuppressant drugs. 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. A magnetic resonance imaging (MRI) scan may find lesions in the brain before these symptoms develop.

In an [August 2013 Drug Safety Communication](#), we reported that a patient developed PML after taking Gilenya. PML could not be conclusively linked to Gilenya in this case because prior to Gilenya treatment the patient had been treated with an immunosuppressant drug that can cause PML and during Gilenya treatment the patient had received multiple courses of intravenous corticosteroids, which can weaken the immune system.

Gilenya's manufacturer, Novartis, recently notified FDA about one patient with PML and one patient with probable PML that occurred during Gilenya treatment without prior or concurrent exposure to other immunosuppressant drugs. The patient with probable PML did not have clinical signs or symptoms suggestive of PML, and was diagnosed based on MRI findings

compatible with PML and JC virus detected in the cerebrospinal fluid (CSF). The other patient was diagnosed with definite PML based on characteristic symptoms, MRI findings, and JC virus in the CSF. Gilenya treatment was stopped in both patients (see Data Summary). Information describing these two cases has been added to the *Warnings and Precautions* and *Patient Counseling Information* sections of the drug label, as well as to the patient Medication Guide.

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

### **Facts about Gilenya (fingolimod)**

- Gilenya is an immunomodulator used to treat relapsing forms of multiple sclerosis (MS), a brain and spinal cord disease in which patients experience episodes of weakness, numbness, and other nervous system signs and symptoms that partially or completely resolve over weeks or months. Patients with MS may develop persistent symptoms and disability over time.
- An estimated total of approximately 54,000 patients were dispensed Gilenya prescriptions from U.S. mail-order and outpatient retail pharmacies since drug approval in September 2010 through July 2015.<sup>1</sup>

### **Additional Information for Patients and Caregivers**

- One patient has developed progressive multifocal leukoencephalopathy (PML) after taking Gilenya, and one patient has developed probable PML.
- 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.
- Seek medical attention immediately if you experience symptoms that concern you, such as:
  - new or worsening weakness
  - trouble using your arms or legs
  - changes in thinking, eyesight, strength, or balance
- Do not stop taking Gilenya without first talking to your health care professional.
- Read the [Medication Guide](#) you receive with your Gilenya prescription.
- Discuss any questions or concerns about Gilenya and the risk of PML with your health care professional.
- Report side effects from Gilenya to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

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

- Novartis, the manufacturer of Gilenya, reported one case of progressive multifocal leukoencephalopathy (PML) and one case of probable PML in MS patients who were being treated with Gilenya. The patients had no history of prior immunosuppressant

therapy for MS or any other indication. One patient was asymptomatic, but both had positive MRI findings and JC virus in the cerebrospinal fluid (CSF).

- Prior cases of PML in patients taking Gilenya were confounded by immunosuppressant use before or concurrent with the drug.
- Tell patients taking Gilenya to contact you if they develop any symptoms that may be suggestive of PML. Symptoms of PML are diverse, progress over days to weeks, and can lead to severe disability or death. Symptoms can include the following:
  - progressive weakness on one side of the body or clumsiness of limbs
  - disturbance of vision
  - changes in thinking, memory, and orientation
  - confusion or changes in personality
- MRI signs of PML may be apparent before clinical symptoms develop.
- Stop Gilenya immediately at the first sign or symptom suggestive of PML and perform an appropriate diagnostic evaluation.
- Report adverse events involving Gilenya to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

## Data Summary

Novartis, the manufacturer of Gilenya, reported to FDA that one patient developed progressive multifocal leukoencephalopathy (PML) and one patient developed probable PML after taking the drug. Neither patient had prior exposure to or concomitant treatment with other immunosuppressants for MS or any other medical condition. Gilenya treatment was stopped in both patients. These cases are described below.

### Case #1:

A 49-year-old developed probable PML after taking Gilenya for approximately four years. The patient had a 5-year history of multiple sclerosis (MS) and had previously been treated for relapse with Rebif (interferon beta-1a) for 10 months in addition to short-term corticosteroids, before and during Gilenya treatment. The patient had not received Tysabri (natalizumab), a known cause of PML, or other drugs known to alter immune function. After Rebif was discontinued, the patient took Gilenya for approximately 4 years prior to undergoing routine Magnetic Resonance Imaging (MRI), in which lesions considered atypical for MS and compatible with PML were detected. The lesions were new when compared to an MRI conducted prior to starting Gilenya. A CSF sample taken at that time was positive for JC virus DNA. The drug was discontinued. The diagnosis of probable PML was based on MRI findings and the detection of JC virus DNA in the CSF in the absence of clinical signs or symptoms specific to PML. This diagnosis of probable PML is consistent with diagnostic criteria outlined in the American Academy of Neurology consensus statement (Berger J, et al. *Neurology* 2013; 80;1430-1438).

### Case #2:

A 54-year-old developed PML after taking Gilenya for approximately 2.5 years. The patient had a 13-14 year history of MS and had previously been treated with interferon beta-1b for approximately 11 years. The patient had also been treated with mesalazine for ulcerative colitis for the last 4 years. Neither interferon beta-1b nor mesalazine are known causes of PML. Two

and a half years prior to developing PML, therapy for MS was switched from interferon beta-1b to Gilenya. The drug was discontinued and the patient was hospitalized with suspected PML after developing new symptoms, including walking instability, clumsiness, inattention, somnolence and mental sluggishness. At that time, a brain MRI was suggestive of PML, and JC virus DNA was detected in the CSF. The diagnosis of PML in this patient was based on symptoms, characteristic MRI findings, and the detection of JC virus DNA in the CSF.

## **Reference**

1. Symphony Health Solutions' Integrated Dataverse (IDV). Sep 2010 – July 2015. Extracted July 2015.