



FDA warns about severe worsening of multiple sclerosis after stopping the medicine Gilenya (fingolimod)

Safety Announcement

[11-20-2018] The Food and Drug Administration (FDA) is warning that when the multiple sclerosis (MS) medicine Gilenya (fingolimod) is stopped, the disease can become much worse than before the medicine was started or while it was being taken. This MS worsening is rare but can result in permanent disability. As a result, we have added a new warning about this risk to the prescribing information of the Gilenya [drug label](#) and patient [Medication Guide](#).

Gilenya is one of several medicines approved to treat a form of MS called relapsing MS, which are periods of time when MS symptoms get worse. The medicine was approved in the United States in 2010.

Health care professionals should inform patients before starting treatment about the potential risk of severe increase in disability after stopping Gilenya. When Gilenya is stopped, patients should be carefully observed for evidence of an exacerbation of their MS and treated appropriately. Patients should be advised to seek immediate medical attention if they experience new or worsened symptoms of MS after Gilenya is stopped.

Patients should contact your health care professional immediately if you experience new or worsened symptoms of MS after Gilenya treatment is stopped. These symptoms vary and include new or worsened weakness, increased trouble using arms or legs, or changes in thinking, eyesight or balance. Gilenya treatment may have to be stopped for reasons such as adverse drug reactions, planned or unplanned pregnancy, or because the medicine is not working. However, patients should not stop taking it without first talking to their prescribers, as stopping treatment can lead to worsening MS symptoms.

In the 8 years since Gilenya was approved in September 2010, we identified 35 cases of severely increased disability accompanied by the presence of multiple new lesions on magnetic resonance imaging (MRI) that occurred 2 to 24 weeks after Gilenya was stopped. Most patients experienced this worsening in the first 12 weeks after stopping. Our analyses include only reports submitted to FDA* and those found in the medical literature, so there may be additional cases about which we are unaware. The severe increase in disability in these patients was more severe than typical MS relapses, and in cases where baseline disability was known, appeared unrelated to the patients' prior disease state. Several patients who were able to walk without assistance prior to discontinuing Gilenya progressed to needing wheelchairs or becoming totally bedbound. In patients experiencing worsening of disability after stopping Gilenya, recovery varied. Seventeen patients had partial recovery, 8 experienced permanent disability or no

recovery, and 6 eventually returned to the level of disability they had before or during Gilenya treatment.

We previously communicated safety information about Gilenya in [August 2015](#) and [August 2013](#) (rare brain infection), [May 2012](#) (revised cardiovascular monitoring recommendations), and [December 2011](#) (safety review of reported death).

To help FDA track safety issues with medicines, we urge health care professionals and patients to report side effects involving Gilenya and other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

*[FDA Adverse Event Reporting System \(FAERS\) database](#).

Facts about Gilenya (fingolimod)

- Gilenya is one of several medicines used to treat relapsing multiple sclerosis (MS).
- Gilenya is available as 0.5 mg capsules. It is taken once daily by mouth.
- Common side effects include cough, headache, back pain, and diarrhea.
- In addition to the increase in disability that can occur after Gilenya discontinuation described here, Gilenya can cause a number of other serious adverse reactions that are already included in the prescribing information such as:
 - Slow heart rate called bradycardia, or with an abnormal heart rhythm called bradyarrhythmia
 - Infections, including a rare brain infection called progressive multifocal leukoencephalopathy
 - Swelling in the eye called macular edema, which causes vision problems

Additional Information for Patients and Caregivers

- FDA is warning that when Gilenya is discontinued, symptoms of disability and other effects of multiple sclerosis (MS) can become worse than they were before or during Gilenya treatment. This severe disease worsening is rare but can result in permanent disability.
- Gilenya treatment may have to be stopped for reasons such as drug adverse reactions, planned or unplanned pregnancy, or because the medicine is not working.
- Because of this disease worsening, do not stop taking Gilenya without first talking to your health care professional.
- Seek medical attention immediately if you experience worsening symptoms after stopping Gilenya such as:
 - new or worsening weakness
 - increased trouble using your arms or legs
 - changes in thinking
 - changes in eyesight
 - changes in strength or balance
- In addition to severe MS worsening after discontinuation, Gilenya may cause other serious adverse reactions. These known risks are listed in the patient [Medication Guide](#),

which explains the benefits and risks of the medicine. This guide has been updated to include severe MS worsening after discontinuation. It is important for you to read the Medication Guide that comes with each Gilenya prescription because the guide is updated as new information becomes available. Other serious adverse reactions include:

- Slow heart rate, called bradycardia or bradyarrhythmia
- Infections, including a rare brain infection called progressive multifocal leukoencephalopathy
- Swelling in the eye called macular edema, which causes vision problems
- To help FDA track safety issues with medicines, report side effects from Gilenya or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is warning that discontinuation of Gilenya treatment in rare instances may result in a severe increase in disability accompanied by the presence of multiple new lesions on MRI. The increase in disability is severe and potentially irreversible.
- A new warning about this risk has been added to the prescribing information of the Gilenya [drug label](#) and patient [Medication Guide](#).
- Before initiating Gilenya treatment, inform patients about the potential risk of severe increase in disability when Gilenya is discontinued.
- Test for new or enhancing lesions by magnetic resonance imaging (MRI) if an increase in disability occurs and begin appropriate treatment as needed.
 - In the eight years since Gilenya’s 2010 approval, FDA received 35 cases of severe increase in disability accompanied by the presence of multiple new gadolinium-enhancing lesions on MRI following the discontinuation of Gilenya. All 35 patients received corticosteroids as the initial treatment. Of the six patients who were reported to have experienced a full recovery, 3 received only intravenous methylprednisolone, and the other 3 received plasma exchange, intrathecal triamcinolone, or re-started Gilenya. Other patients were also treated with plasma exchange, natalizumab, Gilenya, cyclophosphamide, rituximab, dimethyl fumarate, glatiramer, and methotrexate.
- Gilenya may cause other serious adverse reactions such as:
 - Bradyarrhythmia and atrioventricular blocks
 - Infections, including progressive multifocal leukoencephalopathy
 - Macular edema
- Encourage patients to read the patient [Medication Guide](#) they receive with their Gilenya prescriptions, which explains the benefits and risks of the medicine.
- To help FDA track safety issues with medicines, report adverse events involving Gilenya or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

Data Summary

FDA identified 35 cases of severe increase in disability accompanied by the presence of multiple new gadolinium-enhancing lesions on magnetic resonance imaging (MRI) following the

discontinuation of Gilenya reported in the [FDA Adverse Event Reporting System \(FAERS\) database](#) and the medical literature from September 2010 through February 2018. Twenty-nine cases described symptoms of severe increase in disability beginning less than 12 weeks after Gilenya was discontinued, and six cases described symptoms beginning between 12 and 24 weeks after Gilenya was discontinued. Diagnosis was based on MRI findings of multiple new gadolinium-enhancing lesions in the brain beyond baseline, and severe neurological symptoms based on clinical judgment or Expanded Disability Status Scale (EDSS) score worsening of any magnitude.

The time on Gilenya prior to discontinuation ranged from 7 months to 96 months in these patients. The most common reason for discontinuing Gilenya was that patients intended to become pregnant or had become pregnant. Other reasons for discontinuation included lack of efficacy, lymphopenia, infections, or cancer.

Patient outcomes after the severe increase in disability following Gilenya discontinuation varied. Of the 31 patients with adequately documented outcomes, 6 had a full recovery (reported as either a return to EDSS score reported while on Gilenya or “complete recovery”), 17 had a partial recovery, and 8 had permanent disability or no recovery.

EDSS scores were available for 18 patients while on Gilenya or immediately after discontinuation, and at the time of peak increase in disability after Gilenya discontinuation. The change from EDSS on Gilenya to peak worsening in EDSS after discontinuation ranged from 1.0 to 8.5 (mean change was 2.5). Five of the 18 patients had a worsening of EDSS to ≥ 8.0 at the time of peak worsening after discontinuation which means a patient is essentially restricted to a bed or wheelchair for most of the day.

Treatments for increased disability varied; however, all 35 patients received corticosteroids as the initial treatment. Of the six patients who were reported to have experienced a full recovery, three received only intravenous methylprednisolone, and the other three received plasma exchange, intrathecal triamcinolone, or re-started Gilenya. Other patients were also treated with plasma exchange, natalizumab, Gilenya, cyclophosphamide, rituximab, dimethyl fumarate, glatiramer, and methotrexate. We have not determined the best approach to discontinuing treatment or the best way to treat a severe increase in disability if it occurs.

Related Information

- [Fingolimod \(marketed as Gilenya\) Information](#)
- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)