**What is the medication?**

**Generic:** Fingolimod

**Brand name:** Gilenya
First oral medication approved by the Food and Drug Administration (FDA) to modify the disease course in multiple sclerosis (MS)

**Has the medication received FDA approval?**

Yes – 0.5 mg daily dose approved on September 21, 2010

**If so, what are the indications and uses (e.g., types of MS)?**

- Indicated to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability in patients with relapsing forms of MS
- Studies currently underway to determine its potential benefit for persons with primary-progressive MS

**What were the findings in the pivotal trials of this medication? (For whom has it shown benefit? For whom might it prove harmful? For whom do we have no data?)**

Two pivotal trials have been published to date, both in the February 4, 2010, issue of the *New England Journal of Medicine*:


  **Trial design:** In a 24-month study, two doses of fingolimod (0.5 mg and 1.25 mg) were compared to placebo in 1272 individuals with relapsing-remitting MS in whom at least one relapse was documented in the year prior to entry or at least two relapses in the 2 years prior to entry, and who were ambulatory without support (Expanded Disability Status Scale [EDSS] <6.0). If the individual was on treatment with interferon beta or glatiramer acetate prior to entry into the trial, the medication was stopped for at least 3 months prior to randomization.

  **Primary endpoint:** The primary study endpoint was annualized relapse rate based on confirmed relapses with changes in objective neurologic findings documented by a study investigator.
Key secondary endpoint:
- Time to confirmed progression of one point or more on the EDSS (0.5 point if starting at EDSS 5.5) confirmed after 3 months.

Other secondary endpoints:
- Time to first relapse
- Time to disability progression confirmed after 6 months
- Changes in EDSS and Multiple Sclerosis Functional Composite (MSFC) between baseline and 24 months
- MRI disease measures, including new or enlarged T2 lesions, gadolinium enhancing lesions, T1 hypointense lesions, brain volume changes
- Safety and tolerability measures

Results:
- About 81% of the initially enrolled subjects completed the study.
- Annualized relapse rate (primary outcome): 0.18 for the 0.5 mg fingolimod group, 0.16 for the 1.25 mg fingolimod group, and 0.40 for the placebo group, representing a relative risk reduction of 54% for the 0.5 mg dose group as compared to placebo.
- On time to EDSS progression sustained for 3 months (key secondary endpoint): 30% relative risk reduction favoring 0.5 mg fingolimod over placebo.
- Other secondary clinical measures of relapse and risk of EDSS progression also favorably affected by the 0.5 mg–dose of fingolimod compared to placebo.
- Differences between the 0.5 mg– and 1.25 mg dose arms on clinical measures were not significant.
- The mean (median) number of T1 gadolinium contrast-enhancing lesions at month 24 of the study were 0.2 (0) in those on the approved 0.5 mg dose of fingolimod compared to 1.1 (0) in those taking the placebo (0<0.001). The mean (median) number of new or newly-enlarging T2 lesions over the 24 months of the study were 2.5 (0) for the fingolimod 0.5 mg group compared to 9.8 (5.0) for those in the placebo group (p<0.001).


Trial design: In a 12-month comparison trial, 1292 patients with relapsing-remitting MS who had a relapse within 12 months prior to entry, or two relapses within 2 years of entry (whether on interferon beta, glatiramer acetate, or no disease-modifying agent), were randomly assigned to one of three groups:
- interferon beta-1a 30 mcg IM once weekly + oral placebo
- 0.5 mg of fingolimod once daily + IM placebo injection once weekly
- 1.25 mg of fingolimod orally once daily + IM placebo injection once weekly.
Primary endpoint: annualized relapse rate over the 12-month period of the trial as defined in FREEDOMS I above

Key secondary endpoints:
- Number of new or enlarged T2 lesions on MRI at 12 months compared to baseline
- Time to EDSS progression as defined in the FREEDOMS study above

Results:
- Eighty-seven percent of the subjects completed the 12-month study on their allocated treatment.
- Annualized relapse rate (primary outcome): 0.16 for the 0.5 mg fingolimod group; 0.20 for the 1.25 mg fingolimod group; 0.33 for the interferon beta group, representing a 52% relative risk reduction for the 0.5 mg dose as compared to interferon beta-1a 30 mcg IM once weekly.
- Of those participating in the study, 70.1% of the interferon beta group and 82.5% of the fingolimod 0.5 mg group had no relapses during the 12 months of observation.
- The mean (median) number of T1 gadolinium contrast-enhancing lesions at month 12 were 0.2 (0) for the approved 0.5 mg dose of fingolimod compared to 0.5 (0) for interferon beta-1a 30mcg IM (p<0.001).
- The mean (median) number of new or newly enlarging T2 lesions over the 12 months of the study were 1.6 (0) for the group receiving 0.5 mg fingolimod compared to 2.6 (1.0) for the group receiving interferon beta -1a 30mcg IM (p=0.002).
- About 90% of patients in all arms had no disability progression, and no differential effect on EDSS was demonstrated in this study.

What is the mechanism of action and the rationale for its use in MS?

- Fingolimod is a new class of MS medication that acts by modulating sphingosine-1-phosphate receptors on cell surfaces.
- It is thought to affect four of the five known subtypes of S1P-1 receptors following phosphorylation in the body.
- Binding of fingolimod-phosphate results in internalization and degradation of the S1P receptor and loss of its signaling functions.
- Binding to S1P-1 receptors supplies signals necessary for lymphocyte egress from lymph nodes into the circulation. Loss of this binding due to absence of the receptor results in sequestration of lymphocytes in the lymph nodes.
- Effects appear to be different in lymphocyte subtypes, resulting in sequestration of naïve and central memory T cells but not effector memory cells.
- S1P receptors are present in numerous cell types in the body, including glial and neuronal cells. It is not currently known if fingolimod has beneficial effects related to actions on human CNS cells.


What is the delivery route and recommended dosing?

0.5 mg orally once daily

Can this medication be used with other medications?

- Disease-modifying Therapies (DMT):
  - Has this medication been tested in combination with other medications?
    - No studies have evaluated the use of fingolimod in combination with other disease-modifying therapies.
    - The effects of antineoplastic, immunosuppressive, or immunomodulating therapies are expected to increase the risk of immunosuppression with fingolimod.
    - Caution is advised when switching patients from long-acting therapies such as natalizumab or mitoxantrone to fingolimod. See Product Insert.

- Other Medications
  - Are there potential concerns regarding concurrent or prior use of other medications?
    - Experience with fingolimod in patients receiving concurrent therapy with beta blockers or in those with a history of syncope is limited. Fingolimod has not been studied in: patients with sitting heart rate less than 55 bpm; patients with second degree or higher AV block, sick sinus syndrome, prolonged QT interval, ischemic cardiac disease, or congestive heart failure; or patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic drugs. Class Ia and Class III antiarrhythmic drugs have been associated with cases of torsades de pointes in patients with bradycardia.
    - Certain antifungal agents such as ketoconazole increase blood levels of fingolimod and may potentiate adverse reactions.
Live vaccines should not be used in patients receiving fingolimod or within 2 months of stopping fingolimod, due to risk of infection.

Vaccination with inactivated vaccine formulations may be less effective during treatment and for 2 months afterward.

How does the expected treatment effect compare to the treatment effect provided by other available medications?

- Only one comparative study is available – see information about the TRANSFORMS trial above.
- Available data do not allow firm conclusions about the relative effectiveness of fingolimod and beta interferons or glatiramer acetate given subcutaneously. Head-to-head comparative studies will be needed to determine their relative effectiveness.

What are the possible short-term side effects? What is the range of severity of these side effects and what are the recommended management strategies?

- The first dose of fingolimod typically results in a bradycardia that peaks 6 hours after dosing. The bradycardia rarely (0.5%) results in symptoms. It is recommended that the patient be observed for the first six hours after the first dose of fingolimod and treated supportively if symptomatic bradycardia occurs. The bradycardia is rarely (0.1%) associated with atioventricular conduction block. The safety of fingolimod for patients with pre-existing heart disease and those being treated with class Ia (e.g. quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic drugs is unknown. Therefore, it is recommended that fingolimod be used with caution in these individuals.
- The most common side effects in the pivotal trials were headache, influenza, diarrhea, back pain, liver abnormalities, and cough.

What are the known and theoretical long-range (morbidity and mortality) health risks?

The known long-range side effects include increased risk for infections, macular edema, decrease in pulmonary function, elevated serum hepatic transaminases, and embryo-fetal death and malformations. These are listed in the Product Insert.

- Infection: While the overall rate of infections (72%) and serious infections (2%) on the recommended (0.5 mg) dosing of fingolimod was similar to placebo, the rates of bronchitis and pneumonia were somewhat higher in the fingolimod group – and two patients on the higher dose of fingolimod (1.25 mg daily) died of herpetic infections, one of whom lacked immunity to varicella-zoster virus (VZV).

In patients without a history of chickenpox or varicella vaccination, antibody testing and vaccination of antibody-negative patients should be considered before the
initiation of fingolimod treatment. Fingolimod has not been used in patients taking other immunosuppressive treatments. It is recommended that fingolimod not be started in patients with active acute or chronic infections.

- **Macular edema**: Because macular edema occurred in 0.4% of treated patients, it is recommended that patients undergo ophthalmologic evaluation at baseline and at 3 to 4 months of treatment. Additional ophthalmologic evaluations should be undertaken if visual symptoms occur. The risks of macular edema in patients with a history of uveitis or diabetes mellitus appear higher, and periodic monitoring for macular edema is recommended in such patients.

- **Decrease in pulmonary function**: Dose dependent reductions in FEV1 and carbon monoxide diffusion capacities were observed in patients on fingolimod. These reductions increased with duration of therapy. The changes were rarely symptomatic – with only a few patients discontinuing therapy due to dyspnea – and the changes in FEV1 appeared to be reversible upon discontinuation of therapy. Use in patients with compromised pulmonary function has not been tested.

- **Elevated serum hepatic transaminases**: Elevations in transaminases were observed more frequently in patients on fingolimod than on placebo. Most elevations occurred at 3 to 4 months of treatment and returned to baseline if treatment was discontinued. It is recommended that transaminase and bilirubin determinations be obtained prior to starting treatment and repeated if symptoms suggestive of hepatic dysfunction occur. Patients with preexisting liver disease may be at increased risk of hepatotoxicity with fingolimod.

- **Fetal death and malformations**: Animal studies suggest that fingolimod may cause fetal harm, including embryo-fetal death and fetal malformations. Effective contraception should be used during fingolimod treatment in women with childbearing potential. Women who wish to become pregnant should be counseled that it takes approximately 2 months to clear fingolimod after discontinuing treatment, so they should avoid becoming pregnant within that period.

- **Hypertension and Cardiovascular System**
  In clinical trials with fingolimod, a small sustained increase in blood pressure was seen after 2 months of continued therapy. The increase averaged approximately 2mm Hg systolic and 1mm Hg diastolic blood pressure. Hypertension was reported as an adverse reaction in 5% of patients on fingolimod 0.5mg and 3% on placebo. Vascular events including ischemic and hemorrhagic strokes, peripheral arterial occlusive disease, and posterior reversible encephalopathy syndrome (PRES) have been reported in clinical trials with higher doses of fingolimod, but were not observed with the 0.5mg dose as of September 2010.
Has the FDA included any black box warnings about this medication?

No

What training is recommended or required for patients and clinicians before initiating this treatment?

There is no specific training required of either provider or patient before initiating fingolimod treatment.

What is the pregnancy rating for this medication, and what is known about possible carcinogenesis, mutagenesis, and impairment of fertility?

Fingolimod is Pregnancy Category C; based on animal data, may cause fetal harm.

Does this medication interact or interfere with oral contraceptives?

Fingolimod is not known to interact with oral contraceptives.

Has the FDA recommended or required a safety-monitoring program?

- 5000-patient 5-year follow-up registry required to monitor for emergent adverse effects
- Pregnancy registry established

What kind of safety monitoring is recommended (including prescreening, routine check-ups, and laboratory tests)?

- The FDA has recommended measurement of baseline pulse and blood pressure just before the first dose of fingolimod and observation of all patients for 6 hours after the first dose for signs and symptoms of bradycardia. If patient becomes symptomatic, repeat pulse and blood pressure measurement, assess need for additional monitoring procedures or clinical intervention, and continue observation until the symptoms have resolved.
- Blood pressure should be monitored during treatment with fingolimod.
- The FDA has recommended that patients being considered for fingolimod treatment undergo white blood cell count, serum transaminase determination, serum bilirubin determination, serum varicella zoster antibody testing (in patients with no history of chicken pox), baseline ECG, and ophthalmologic evaluation.
• During treatment, all patients should undergo ophthalmologic evaluation after 3 to 4 months of treatment and in the event of new visual symptoms.
• Patients who develop symptoms of respiratory or hepatic disease while on treatment should undergo appropriate evaluations (e.g., pulmonary function testing for symptoms of pulmonary disease).

Are there any recommended limits on duration of treatment with this medication?

There are no recommended limits to the duration of treatment with fingolimod.

What happens following termination of treatment with this medication?

• What treatment options are available for patients after being treated with fingolimod?
  
  Other disease-modifying therapies.

• What is the wash-out period?
  
  Unknown. Lymphocyte levels generally return to normal within 2 months following discontinuation of fingolimod.

How can a provider identify a suboptimal treatment response?

• Clinical assessment, neuroimaging (MRI), and patient self-report
• Continued MS disease activity in a patient adherent to treatment

Is the manufacturer/distributor offering any financial assistance program for patients?

Financial assistance available from Novartis (clinicians contact GILENYAsupport.com; patients call 1-877-408-4974)

Are there any special considerations for this drug?

People with relapsing forms of MS would be appropriate candidates for this therapy.
COMMENTARY BY TEMPLATE AUTHORS

- Treatment could be continued indefinitely unless discontinuation is required because of persistent disease activity or unacceptable side effects or toxicity.

- Providers should be familiar with the potential adverse effects of fingolimod, and patients should be counseled on the symptoms of those adverse effects and told to contact their provider if they experience any of them.

- It is recommended that all individuals being considered for fingolimod be tested for antibodies to VZV, irrespective of prior history, to ensure adequate immunity. In those who are immunized in order to start treatment, there should be a delay of at least one month between vaccination and treatment.

- Some MS clinicians recommend periodic ophthalmologic monitoring in all patients receiving fingolimod.

- Individuals with a history of cardiac disease or with silent prolongation of the QT interval were excluded from the clinical trials, and the risk of adverse cardiac effects in such patients when receiving fingolimod is unknown.

- In TRANSFORMS but not in FREEDOMS I, an increased number of cutaneous malignancies were observed in the fingolimod groups. Although not itemized in the warnings, some MS clinicians recommend baseline and periodic screening for cutaneous malignancies in patients starting fingolimod.

WEB LINKS PROVIDED IN THIS DOCUMENT

Fingolimod (Gilenya) Update for Clinicians and People Affected by MS

Update Posted on February 10, 2012

Following the report on January 20, 2012 of 11 deaths among patients who received fingolimod (Gilenya) outside of the clinical trials, the European Medicines Agency (EMA) announced a review of the medication. This review is separate from the investigation currently underway by the U.S. Food and Drug Administration (FDA). The FDA issued a statement in December, 2011 concerning a patient who died within 24 hours of receiving a first dose of the medication.

According to Novartis Pharmaceuticals, more than 33,000 people have received fingolimod to date. Although little is known at this time about the 11 reported deaths, they appear to be related to cardiac events. Until the EMA and FDA have completed their reviews, it is impossible to know what role fingolimod may have played in the deaths.

While their review is under way, the EMA has recommended to healthcare professionals in Europe that they increase patient monitoring for the first dose of fingolimod. The recommendations include:

- Electrocardiogram (ECG) monitoring before treatment and then continuously during the first six hours following the first dose
- Measurement of blood pressure and heart rate every hour during the six-hour observation period
- After six hours, any patients with clinically important heart-related effects, such as bradycardia (a slow heart rate) or atrioventricular block (a problem with the conduction of electricity in the heart), should continue to be managed and monitored until their condition has improved.

Pending further investigation, the FDA recommends that healthcare professionals who prescribe Gilenya continue to follow the recommendations on the approved label. The FDA further states that people who are currently taking Gilenya should not stop taking it without talking to their prescriber.

The Emerging Therapies Collaborative will continue to post updated information as it becomes available.

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The Emerging Therapies Collaborative is proud to be a source of information about multiple sclerosis. Our comments are based on published data and expert opinion, but do not represent individual therapeutic recommendations or prescriptions. For specific information and advice, consult your physician.