

## Mellen Center Approaches: Use of fingolimod in MS (Gilenya, FTY720)

### What is Gilenya and how does it work?

Gilenya (fingolimod, FTY720) was approved by the US FDA in September 2010 as the first oral disease modifying treatment for MS.(1) Combined data from a Phase II study and two Phase III trials showed that Gilenya reduces relapses, disability progression, MRI lesion activity, and brain atrophy progression (loss of brain tissue).(2-4)

Gilenya is a sphingosine 1-phosphate receptor (S1PR) modulator. By decreasing S1PRs on T-cells and B-cells it blocks their egress from lymph nodes and interferes with recirculation to the central nervous system (CNS), thus reducing inflammatory lesion activity. Additional immunologic and direct CNS effects may also contribute to efficacy. Interaction of Gilenya with S1PRs on a variety of other cell types in other tissues account for its potential adverse effects.

### How is Gilenya administered?

Gilenya is administered as a once-per-day 0.5-mg capsule. Food does not alter Gilenya absorption. Therefore, it can be taken without regard to meals.

### For whom should Gilenya be considered?

Gilenya was approved to reduce relapses and disability progression in patients with relapsing forms of MS. For patients with ongoing disease activity, intolerable side effects, or logistical issues with the previously-available MS therapies, Gilenya is an appropriate option.

### Should Gilenya be used as initial MS therapy?

Although Gilenya is approved as first line therapy (i.e. patients are not required to have tried other medications before Gilenya), long-term experience with its use is limited. Therefore, as experience with Gilenya accumulates, Mellen clinicians currently plan to recommend interferon-beta or glatiramer acetate

as initial therapy for most patients. It is reasonable to consider Gilenya as initial therapy for patients who are averse to injection.

### Should patients switch from a previously-available injected medication to Gilenya?

We anticipate many patients currently on an injectable therapy will be attracted to Gilenya's oral route of administration. However, if a patient is stable clinically and radiographically, and he/she is not experiencing significant adverse effects, in general, we recommend not switching therapy until we have more experience with Gilenya.

For JC virus antibody-positive patients on Tysabri who are concerned about the risk of progressive multifocal leukoencephalopathy, Gilenya is a reasonable consideration.

### What side effects and safety issues does Gilenya have?

Gilenya is generally safe and well tolerated. However, several safety issues have been noted:

- 1. Slowing of heart rate and atrioventricular block.** Heart rate consistently slows following administration of the 1<sup>st</sup> dose of Gilenya, and rarely slowing of atrioventricular (AV) conduction may occur. Typically these changes are asymptomatic, reach a maximum 4-5 hours after the 1<sup>st</sup> dose, subsequently improve even with continued dosing, and return to baseline over the 1<sup>st</sup> 1-2 weeks. Very rarely, patients develop symptoms (lightheadedness, dizziness, palpitations, chest pain, etc.) or more worrisome abnormalities on the EKG (i.e., 2nd degree AV block), and very rarely require intervention.

Patients receiving Class Ia anti-arrhythmics (e.g. quinidine, procainamide) or Class III anti-

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arrhythmics (e.g. amiodarone, sotalol), beta blockers, or calcium channel blockers; patients with pre-existing slow heart rate, sick sinus syndrome, AV block, ischemic heart disease, or congestive heart failure; and patients with a past history of syncope are at increased risk of bradycardia and/or AV block with initiation of Gilenya.

Monitoring patients in a physician's office for signs and symptoms of bradycardia or AV slowing for 6 hours after the 1<sup>st</sup> dose is required. If a patient stops Gilenya for 2 weeks, monitoring will be required again when it is restarted.

- 2. Macular edema.** Rarely, patients treated with Gilenya develop macular edema, manifested clinically as blurred vision. It usually develops within 3-6 months after starting Gilenya and improves or resolves with discontinuation of Gilenya. Patients with diabetes and uveitis are at increased risk for macular edema from Gilenya. Patients should have an eye exam including optical coherence tomography (OCT) prior to starting Gilenya, and 3-4 months after starting treatment. Patients should be instructed to notify their care team if they develop blurred vision after starting Gilenya.
- 3. Liver Abnormalities.** Gilenya rarely causes elevation of liver transaminases, typically mild and reversible. Although the FDA does not require monitoring liver function tests, we anticipate checking ALT and AST prior to starting Gilenya and after approximately 3 and 6 months of therapy.
- 4. Increased blood pressure.** Blood pressure typically increases mildly during the first 6 months of treatment with Gilenya then stabilizes. Patients with known hypertension should have their BP monitored while on Gilenya and their anti-hypertensive regimen adjusted as needed. Gilenya should be used with caution in patients with poorly controlled hypertension.
- 5. Infections.** Gilenya is a potent immunomodulatory drug and reversibly lowers blood lymphocyte counts. Although an increased number or severity of infections was not seen in an integrated analysis of the Gilenya clinical trial program, infection would not be an unexpected potential adverse effect. Therefore, patients should be monitored

for infections during Gilenya therapy, and Gilenya should be used with caution in patients with recurrent or chronic infections. Gilenya may increase the risk of serious primary infections, in particularly those due to herpes viruses. Patients should be asked whether they have a history of chicken pox or shingles, and a Varicella zoster IgG titer should be checked if there is no history or uncertain history. Seronegative patients should receive a Herpes zoster vaccine prior to starting Gilenya.

- 6. Pulmonary effects.** Gilenya rarely causes decreased FEV<sub>1</sub> or D<sub>L</sub>CO, which typically are mild, develop as early as 1 month after treatment initiation, and are reversible with drug discontinuation. Routine pulmonary monitoring is not required, but patients who develop shortness of breath or persistent cough should be referred for pulmonary assessment.
- 7. Other rare side effects** include headache, diarrhea, back pain, and vascular disorders.

### What testing is required with Gilenya therapy?

Prior to starting therapy:

- Blood tests - CBC, ALT, AST, pregnancy test, and Varicella zoster IgG titer (if there is no history or uncertain history of chickenpox or shingles).
- Ophthalmology exam with OCT.
- EKG. Consider Cardiology referral if EKG is abnormal and/or there is a history of heart disease.
- Consider Pulmonary referral if there is a history of severe asthma or COPD

1<sup>st</sup> day of therapy (Mandatory First Dose Observation)

- Monitoring for 6 hours in a physician's office. Routinely we perform vital signs prior to administering the first dose, at 3-4 hours, and prior to discharge at 6 hours. EKG is performed at beginning and end of monitoring.
- Patients who develop a heart rate <45 bpm, or a new onset 2nd degree or higher atrioventricular block should be monitored until resolution of the finding. Patients at lowest post-dose heart rate at the end of the observation period should be monitored until heart rate increases.

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- In patients experiencing symptomatic bradycardia, begin continuous ECG monitoring until the symptoms have resolved; if pharmacological intervention is required to treat bradycardia, continuous ECG monitoring should continue overnight in a medical facility, and first-dose monitoring procedures should be repeated for the second dose.
- Patients at higher risk of symptomatic bradycardia or heart block because of a coexisting medical condition or certain concomitant medications should be observed overnight with continuous ECG monitoring (2).
- Patients with prolonged QTc interval at baseline or during the observation period, or taking drugs with known risk of torsades de pointes should be observed overnight with continuous ECG monitoring.

See below for specific prescribing information:

<http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf>

### During therapy

- ALT and AST at 3 and 6 months.
- Ophthalmology exam with OCT at 3-4 months.
- Pulmonary evaluation if the patient develops dyspnea or persistent cough.

### Are there any restrictions on who can take Gilenya?

There are no absolute restrictions. In general, care will be needed for patients with heart disease, history of syncope, recurrent or chronic infections, no history of chicken pox or shingles, uveitis or diabetes, lung disease, liver disease, and poorly controlled hypertension.

Certain medications should not be taken with Gilenya (see below).

No dose adjustment is needed with mild-moderate hepatic or renal impairment. Severe hepatic or renal impairment increase the accumulation of Gilenya or its metabolites, and may increase adverse effects.

Because the participants in Gilenya clinical trials were at least 18 years old, the effectiveness and safety of Gilenya in pediatric patients is not known.

Gilenya clinical trials included few participants 65 years of age or older, so the effectiveness and safety of Gilenya in geriatric patients is not known.

### Does the risk of infection relate to peripheral blood white blood cell or lymphocyte counts?

As a result of inhibiting lymphocyte egress from lymph nodes, peripheral blood lymphocyte counts are rapidly and markedly decreased with Gilenya therapy. However, there is no clear-cut relationship between the level of lymphopenia and incidence or severity of infections. Therefore, monitoring blood counts is not useful to assess the risk of infection.

### Is Gilenya effective in progressive MS?

The effectiveness and safety of Gilenya in primary and secondary progressive MS is not known. An ongoing Phase III trial is evaluating Gilenya in primary progressive MS.

### Is Gilenya safe during pregnancy?

Based on animal studies, Gilenya potentially causes fetal harm and is classified as Pregnancy Category C. Women should use effective contraception while taking Gilenya and for 2 months after stopping it. Women should discontinue Gilenya 2 months prior to attempting to become pregnant.

### Can Gilenya be used in combination with other MS disease therapies?

There are no data concerning the safety or utility of combining Gilenya with other MS disease therapies. Co-administration of Gilenya with immunosuppressant medications would be expected to increase the risk of infection.

### Can Gilenya be combined with MS symptom medications?

Gilenya can be combined with MS symptom medications without problem.

### Can Gilenya be combined with medications for other conditions?

There are some medications used for other conditions that should be combined with Gilenya with caution: Class Ia anti-arrhythmics (e.g. quinidine, procainamide) or Class III anti-arrhythmics (e.g. amiodarone, sotalol), beta-blockers, calcium channel blockers, and the anti-fungal ketoconazole (Nizoral). The patient's medical history and medications should be reviewed in detail prior to starting Gilenya.

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### **Can the dose of Gilenya be increased beyond 0.5 mg per day?**

The approved dose of Gilenya is 0.5 mg per day.

1.25-mg and 5-mg doses were tested in the Gilenya Phase II and Phase III trials. These higher doses were less well tolerated without increased efficacy.

#### REFERENCES

1. NDA 02257 FDA Approved Labeling Text for Gilenya (fingolimod) capsules. September 21, 2010.
2. Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med.* 2006;355:1124-40.
3. Kappos L, Radue E-W, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *New Eng J Med.* 2010;362:387-401.
4. Cohen JA, Barkhof F, Comi G, Hartung H-P, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *New Eng J Med.* 2010;362:402-15.