Brand Name: Gilenya

Generic Name: Fingolimod

Manufacturer[1]: Novartis Pharmaceutical Corporation

Drug Class[1,2]: Sphingosine 1-phosphate receptor modulator

Uses:

Labeled Uses[1,2,3,4,5]: Relapsing forms of multiple sclerosis.
Unlabeled Uses[1,2,3,4,5]: None.

Mechanism of Action[1,2,3,4,5]: Fingolimod's mechanism of action is unknown, but may involve reduction of lymphocyte migration into the central nervous system. An active metabolite of fingolimod, fingolimod-phosphate, modulates sphingosine 1-phosphate receptors and has high affinity for types 1,3,4, and 5 of these receptors. In this way it blocks the capacity of lymphocytes to egress from lymph nodes, causing reduced numbers in peripheral blood.

Pharmacokinetics[1,2,3,4,5]:

Absorption:

T_{max}	12-16 hours
V_d	1200 ± 260 L
$t_{½}$	6-9 days
Clearance	6.3 ± 2.3 L/h
Protein binding	> 99.7%
Bioavailability	93%

Metabolism: Fingolimod is metabolized by three main pathways: reversible stereoselective phosphorylation to the active (*S*)-enantiomer of fingolimod-phosphate, oxidation by the CYP4F2 enzyme and subsequent fatty acid-like break down to inactive metabolites, and formation of inactive non-polar ceramide analogs. Fingolimod is primarily metabolized by CYP4F2 with minor amounts being metabolized by CYP2D6, 2E1, 3A4, and 4F12. The involvement of multiple CYP enzymes suggests that the metabolism of fingolimod would not be subject to substantial inhibition in the presence of an inhibitor of a single specific CYP enzyme.

Elimination: After oral administration, about 81% of the dose is excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are excreted in the feces in amounts of each representing less than 2.5% of the dose.

Efficacy:

Comi G, et al. Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results. Mult Scler. 2010;16(2):197-207.

Study Design: 6 month, randomized, double-blind, placebo-controlled phase II clinical trial followed by an 18 month, re-randomized, double-blinded, mutli-dose extension study, followed by a 12 month open-label, active-drug extension study.

Study Description: *Methods*: Initially, 366 patients were assessed for eligibility, and 281 patients meeting the McDonald criteria for relapsing MS were randomized in a 1:1:1 fashion to receive either fingolimod 5 mg daily, 1.25 mg daily, or placebo. When this core study ended, patients were allowed to continue on into an extension study. In this extension, placebo patients were re-randomized into one of the two treatment groups (dose was blinded from patients and investigators), and treatment group patients stayed at their previously assigned doses until month 15. During months 15-24 patients were switched to the 1.25 mg dose due to a benefit-risk assessment by an independent board indicating lack of increased efficacy and less attractive safety profile at higher doses, and study continued at this dosage to the 36^{th} month. The number of T1 Gd-enhanced lesions and new T2 lesions were assessed via MRI. Trained and certified independent neurologists collected data on relapses and disability from the Expanded Disability Status Scale (EDSS) score at clinical visits every 3 months. Adverse events were recorded and the relationship to the study drug was determined by investigator. *Outcome Results:* At baseline, percent of patients free from Gd-enhanced lesions were 50%, 52% and 48% in the placebo/1.25 mg, 1.25 mg, and 5/1.25 mg groups respectively. At 36 months, these percents were 89%, 88% and 89% respectively. At the end of the core study, patients on fingolimod had significantly fewer T2 lesions than those on placebo. At 36 months the proportion of relapse free patients were 51%, 68%, and 73%, and the proportion of patients free from 6-month disability progression were 80%, 77%, and 76% for the placebo, 1.25 mg and 5/1.25 mg groups respectively. Serious adverse effects were reported in 16% of patients across the 3 treatment groups. Infections were reported in 70% of patients. Seven skin cancers were reported by month 36. Serious cardiac adverse events reported include bradycardia(n=4), palpitations(n=1), arrhythmia(n=1), AV block(n=1), extra systoles(n=1), and ventricular extrasystoles(n=1). In the core study, FEV_1 in the 5 mg group and DL_{CO} in all groups were decreased, but during the extension study these all remained stable within normal range (FEV_1) and around 80% of predicted values (DL_{CO}).

Limitations: This study was limited in that it: lacked a control arm, utilized a high dose of fingolimod, was open-label (in the extension), had reduced evaluable data due to drop outs over the long time period, and allowed potential non-responders to drop out as the extension was optional. Additionally, only two p-values were reported, both from the core study, and all data from this last extension of the study were observed and presented as descriptive statistics only, without any statistical inferential testing.

Conclusion: The results of this elaborate study are quite promising, and it would appear that fingolimod will be useful in the treatment of relapsing multiple sclerosis. Concerning results were the high prevalence of some side effects including skin cancers and infections. However, this is possibly a result associated with the high doses of fingolimod used within this study. Fingolimod was dosed at either 1.25 mg or 5 mg daily originally, then all patients were adjusted to only 1.25 mg daily in this study, but the current approved dosage of this medication is 0.5 mg daily. Given this information, further research at a lower dose is necessary.

Kappos L, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387-401.

Study Design: 24 month, double-blind, multicenter, stratified, randomized, placebo-controlled, parallel group phase III clinical trial

Description of Study: *Methods*: One thousand, two hundred and seventy two patients who met the inclusion/exclusion criteria underwent 1:1:1 randomization into either 0.5 mg or 1.25 mg fingolimod or placebo groups for 24 months. Patients underwent clinical evaluations at screening, randomization, and follow up; Expanded Disability Status Scale (EDSS), Multiple sclerosis functional composite (MSFC), and MRI's were evaluated throughout the study. The primary endpoint was annualized relapse rate, and the key secondary endpoint was disability progression, confirmed after 3 months. Additional secondary endpoints further evaluated relapses, disability progression, and MRI findings. *Outcome Results:* Both treatment groups had lower annualized relapse rates (0.16, 0.18, and 0.40 for 1.25 mg, 0.5 mg and placebo respectively; p-value < 0.001). Also, patients in both treatment groups had higher absence of disability progression, confirmed after three months (83.4±1.9, p-value 0.01; 82.3±1.9, p-value 0.03; and 75.9±2.2% for 1.25 mg, 0.5 mg, and placebo respectively). Other study end points found that both doses of fingolimod showed improvement over placebo in relapse rates, disease progression, and MRI findings. Adverse events that led to study drug discontinuation were more common with 1.25 mg of fingolimod than with the 0.5 mg dose or placebo. Serious adverse events including bradycardia, MS relapse, and basal cell carcinoma, among others, occurred in 10.1, 11.9 and 13.4% of the patients receiving 0.5 mg fingolimod, 1.25 mg fingolimod, or placebo respectively.

Limitations: Utilizing an active comparator or control group, either in place of, or in addition to the placebo group would have strengthened the clinical significance of the study results. Also, study duration was not adequate to evaluate the risks of long term use of fingolimod. Additionally, there is potential for bias, as the drug manufacturer provided study funding, and a few of the authors were employed by the manufacturer. Lastly, the study limited itself in utilizing a higher dose (1.25 mg) than is currently approved.

Conclusion: The results of the study are promising and show that fingolimod possesses comparable safety and increased efficacy in relapse, disability progression, and MRI findings when compared to placebo. Additional research is needed to determine

effectiveness of fingolimod over current standard therapy, but it may play a role in the treatment of relapsing remitting multiple sclerosis.

Cohen J, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402-15.

Study Design: 12 month, double blind, double dummy, multicenter, stratified, randomized, parallel, active control, phase III clinical trial

Description of Study: *Methods*: One thousand, two hundred and ninety two patients who met the inclusion/exclusion criteria were randomized into three groups, 1.25 mg oral fingolimod daily, 0.5 mg oral fingolimod daily, or 30 µg intramuscular interferon β-1a weekly for 12 months. Safety assessments were conducted at screening, randomization and throughout the study; EDSS scores, MSFC scores, and MRI's were evaluated periodically. The primary endpoint was annualized relapse rate, and key secondary outcomes were the number of new or enlarged hyper intense lesions observed on T_2-weighted MRI scans at month 12, and the time to confirmed disability progression. *Outcome Results*: Greater reductions in annualized relapse rates were observed for both fingolimod groups (0.20 for 1.25 mg, 0.16 for 0.5 mg; p-value <0.001) compared to interferon (0.33). Also, patients in both fingolimod groups had fewer new and/or enlarged lesions on T_2-weighted MRI than those in the interferon group (1.5 in the 1.25 mg fingolimod group, p-value < 0.001; 1.7 in the 0.5 mg fingolimod group, p-value = 0.004; and 2.6 in the interferon group). However, there were no significant differences in disability progression among any of the groups (93.3, p-value = 0.5; 94.1, p-value = 0.25; and 92.1% for the 1.25 mg, 0.5 mg and interferon groups respectively). Adverse events described as serious or leading to study drug discontinuation were most common in the 1.25 mg fingolimod group and primarily consisted of bradycardia and atrioventricular block. Additionally, this group had two deaths during the trial; both caused by infection. Other serious infection reported included appendicitis and herpes virus.

Limitations: This study was of a relatively short duration, and so cannot provide long term risk/benefit data of fingolimod versus interferon. Also, the manufacturer funded the study and employed several of the authors. Additionally, the study limited itself by utilizing a higher does (1.25 mg) than is currently approved.

Conclusion: Oral fingolimod showed greater efficacy than interferon therapy in relapse rates and number of lesions, but disability progression was similar in both fingolimod groups and interferon. Studies of longer duration would be useful to evaluate the safety/ tolerability and efficacy of fingolimod with extended use when compared to interferon. In summary, oral fingolimod, particularly at a lower dose (0.5 mg), appears to hold several advantages over IM interferon.

Contraindications[1,2,3,4,5]:

None

Precautions[1,2,3,4,5]:

AV block: Fingolimod therapy may result in transient AV conduction delays which typically resolve within 24 hours of treatment initiation. Recurrence may be observed following discontinuation for more than two weeks and subsequent resumption of therapy.

Bradycardia: Decreased heart rate may occur with initiation of therapy. Heart rate may decrease as soon as one hour after the dose with the maximal decrease occurring approximately six hours after the dose. Heart rate typically returns to baseline after one month of therapy. All patients should be monitored for six hours after the first dose, or in patients where therapy has been interrupted for more than two weeks, for signs/symptoms of bradycardia. In patients who develop bradycardia, appropriate therapy should be initiated and be monitored until symptoms have resolved.

Cardiovascular: Due to the risk of bradycardia and AV conduction delays, ECG is recommended prior to initiation of fingolimod therapy in patients receiving concomitant antiarrhythmics including beta blockers and calcium channel blockers, patients with a slow or irregular heartbeat, or with other cardiac risk factors (eg, second degree or greater AV block, sick sinus syndrome, prolonged QT interval, ischemic cardiac disease, heart failure). If treatment is discontinued for greater than two weeks, repeat ECG is recommended prior to reinitiation.

Hepatic impairment: Use with caution and closely monitor patients with severe hepatic impairment as an increased risk of adverse effects may occur, including elevated liver enzymes. Obtain baseline liver enzymes in all patients prior to therapy initiation, and monitor liver enzymes in patients who develop symptoms of hepatic dysfunction (eg, nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, dark colored urine). Discontinue treatment when liver injury is confirmed. Transaminases tend to normalize within 2 months of discontinuation.

Hypertension: Increased blood pressure may occur approximately two months after initiation of therapy. Patient's blood pressures should be monitored throughout treatment.

Immune suppression: Fingolimod therapy may increase risk of infection due to dose-dependent reduction of lymphocytes. Lymphocyte counts may be decreased for up to two months following discontinuation of therapy. Patients should be monitored for signs and symptoms of infection, and therapy interruption should be considered in patients who develop an infection during therapy. Do not initiate fingolimod treatment in patients with acute or chronic infections until the infection has resolved. Use fingolimod with caution in patients receiving concomitant immunosuppressant, immune modulating, or antineoplastic medications.

Macular edema: May occur, usually in the first three to four months of treatment. Patients may present with blurred vision, decreased visual acuity, or without symptoms. Signs and symptoms generally improve or resolve with discontinuation of treatment. Use fingolimod with caution in patients with a history of diabetes mellitus or uveitis. Ophthalmologic exams should be performed prior to therapy and three to four months after treatment initiation. More frequent examination is warranted in higher risk patients, those with diabetes or a history of uveitis.

Pregnancy and lactation: Fingolimod is a pregnancy category C drug. Pregnancy should be avoided during and for two months after discontinuing treatment to reduce the risk of fetal harm. Excretion of fingolimod into breast milk is unknown, so it is currently not recommended to breast feed while taking fingolimod.

Respiratory effects: Reductions of forced expiratory volume in one second (FEV_1) and diffusion lung capacity for carbon monoxide (DLCO) are dose-dependent and may occur within the first month of therapy. FEV_1 changes may be reversible with drug discontinuation. Fingolimod use in MS patients with compromised respiratory function has not been evaluated, and if clinically necessary, spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy.

Varicella zoster virus (VZV): Consider varicella zoster virus vaccination prior to initiation of fingolimod treatment in VZV-antibody negative patients, and then postpone fingolimod treatment for one month after varicella zoster vaccination.

Adverse Effects[1,2,3,4,5]:

Occurring in >10% of patients:

Central nervous system:
Headache (25%)

Hepatic:
Increased ALT/AST (14%)

Miscellaneous:
Flu-like syndrome (13%)

Gastrointestinal:
Diarrhea (12%)

Neuromuscular & Skeletal:
Back pain (12%)

Occurring in 1 to 10% of patients:

Respiratory:
Cough (10%)
Bronchitis (8%)
Dyspnea (8%)
Sinusitis (7%)

Miscellaneous:

Central nervous system:

Cardiovascular:

Gastrointestinal:

Neuromuscular & Skeletal:

Hepatic:

Dermatologic:

Hematologic:

Ocular:

Endocrine & Metabolic:

Occurring in < 1% of patients:

Ocular:

Macular edema

Drug Interactions[1,2,3,4,5]:

Co-administration with class III antiarrhythmics and class IA antiarrhythmics can cause an increase in risk of bradycardia or heart block. β-blockers, diltiazem, and verapamil may also enhance bradycardia.

Co-administration with live or inactivated vaccines can cause a reduced effectiveness of the vaccine as well as an increased risk of secondary transmission of infection.

Co-administration with ketoconazole may result in increased exposure to fingolimod.

Co-administration with denosumab, leflunomide, natalizumab, pimecrolimus, and tacrolimus may enhance the toxic/adverse effects of these drugs.

Co-administration with Echinacea may decrease the therapeutic effect of fingolimod.

Co-administration with roflumilast may enhance the effects of fingolimod.

Co-administration with sipuleucel-T may decrease the therapeutic effect of this drug.

As fingolimod is metabolized by various CYP enzymes (see Metabolism), there is potential for interactions with inhibitors and/or inducers of these enzymes. Specifically noted are conivaptan, peginterferon α-2b, and tocilizumab.

Dosing/Administration[1,2,3,4,5]:

Adults and Elderly

0.5 mg orally, once daily. Patients should be monitored for 6 hours after the first dose for signs of bradycardia.

Adolescents, children, infants and neonates

No guidelines exist. Safety and efficacy has not been established in patients under 18 years old.

Renal impairment

Dose adjustment is not required.

Hepatic impairment

Dose adjustment is not required with mild or moderate hepatic impairment. Closely monitor in severe impairment as fingolimod exposure is increased.

Conclusion:

Fingolimod has been shown to have increased efficacy when compared to both placebo and weekly IM interferon, and a similar side effect profile to both over 1 and 2 year periods. Also,

fingolimod possess a distinct advantage over IM interferon in that it is administered orally. Currently, further study is needed to assess safety and efficacy over extended periods of time, and a cost benefit analysis comparing fingolimod, IM interferon, as well as other therapeutic interventions for relapsing remitting multiple sclerosis, would be beneficial. Overall, fingolimod appears to be a safe and effective therapeutic option when utilized over 1-2 years for patients with relapsing remitting multiple sclerosis who would prefer oral therapy or who have contraindications to interferon injections.

References:

1) Gilenya [complete prescribing information]. Novartis Pharmaceutical Corporation, Copyright © 2011. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf. Accessed: June 13, 2011.
2) Fingolimod. Clinical Pharmacology [Internet Database]. Elsevier/Gold Standard, 2011. Available at: http://www.clincalpharmacology.com Accessed: June 13, 2011.
3) Fingolimod. Lexi-Drugs[Internet Database]. Lexi-Comp, Inc, 1978-2011. Available at: http://online.lexi.com. Accessed: June 13, 2011.
4) Fingolimod. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: June 13, 2011.
5) Fingolimod. Facts & Comparisons Online [Internet Database]. Wolters Kluwer Health. Available at: http://online.factsandcomparisons.com. Accessed: June 13, 2011.
6) Comi G, et al. Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results. Mult Scler. 2010;16(2):197-207.
7) Kappos L, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387-401.
8) Cohen J, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402-15.

Prepared by: James Neal Ford, PharmD Candidate