Cleveland Clinic Pharmacotherapy Update
From the Department of Pharmacy

Volume XIII, No. V September/October 2010

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Fingolimod: A New Drug for Multiple Sclerosis

By Anthony Zembillas, Pharm.D. Candidate

Introduction: Multiple sclerosis (MS) is a chronic inflammatory disease targeting the central nervous system (CNS). It is theorized that MS is an autoimmune disease in which autoreactive T-cells migrate across the blood-brain barrier and mediate an immune response against central neurons. There are four clinical subtypes of MS: relapsing-remitting MS (RRMS), primary-progressive MS (PPMS), secondary-progressive MS (SPMS), and progressive-relapsing MS (PRMS). Most patients are initially diagnosed with RRMS, which is characterized by variable lengths of symptom-free periods and relapses, indicating new disease activity. During relapses, patients experience worsening symptoms that may last several weeks which may or may not completely resolve. Fingolimod (Gilenya™; Novartis Pharmaceuticals Corporation) was approved by the Food and Drug Administration (FDA) in September 2010 for patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the progression of physical disability.[1] Fingolimod is the first oral drug to reduce MS relapses. Other FDA-approved drugs for relapsing forms of MS must be given by injection either subcutaneously, intramuscularly, or intravenously (See Table 1).[1-8]

Mechanism of Action: Fingolimod is a lipophilic prodrug that is phosphorylated within the CNS to the active metabolite fingolimod-phosphate.[1,9] It has a distinct mechanism of action from other FDA-approved agents for relapsing forms of MS. It acts as a sphingosine-1-phosphate type 1 receptor modulator which induces receptor internalization and renders T and B cells insensitive to a signal necessary for egress from secondary lymphoid tissues. Therefore, recirculation of autoaggressive lymphocytes to the CNS is reduced resulting in decreased CNS inflammation.

Pharmacokinetics: The oral bioavailability of fingolimod is 93%; it can be taken without regard to meals.[1] Approximately 86% of fingolimod is highly distributed into red blood cells. Fingolimod and its active metabolite fingolimod-phosphate are >99.7% protein-bound and are not altered by renal or hepatic impairment. Fingolimod is hepatically metabolized via cytochrome P450 (CYP) 4F2 to fingolimod-phosphate, an active metabolite, along with various inactive metabolites. The half-life of fingolimod and fingolimod-phosphate is approximately 6-9 days. After oral administration, about 81% of the dose is excreted in the urine as inactive metabolites. Both fingolimod and fingolimod-phosphate are eliminated in the feces with each representing less than 2.5% of the drug.

Select Clinical Trials: The efficacy and safety of fingolimod was demonstrated in two randomized, controlled trials. Kappos and colleagues conducted a 2-year, randomized, double-blind, placebo-controlled trial called the **F**TY720 **R**esearch **E**valuating **E**ffects of **D**aily **O**ral Therapy in **M**ultiple **S**clerosis (FREEDOMS).[9] This study included 1,272 patients with a diagnosis of RRMS who had not received interferon-β or glatiramer acetate for at least the previous 3 months. The primary endpoint of this study was the annualized relapse rate, defined as the number of confirmed relapses per year. A key secondary endpoint included the time to disability progression with confirmation after 3 months. Disability progression was defined as an increase of one point in the Expanded Disability Status Scale (EDSS) score confirmed at 3 months with an absence of relapse at the time of assessment. Multiple magnetic resonance imaging (MRI) endpoints evaluated over the 24-month period included number of gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing lesions, and the number of new or enlarged lesions on T_2-weighted MRI scans. Patients were randomized to receive fingolimod 0.5 mg, 1.25 mg, or placebo for up to 24 months. Patients with and without previous disease-modifying therapy receiving fingolimod 0.5 mg and 1.25 mg doses experienced a reduced annualized relapse rate of 54% and 60%, respectively compared with placebo ($p<0.001$). The cumulative probability of disability progression was 17.7% for 0.5 mg of fingolimod, 16.6% for 1.25 mg of fingolimod, and 24.1% for placebo ($p<0.05$ for both fingolimod groups compared to placebo). Both fingolimod groups also had significantly fewer gadolinium-enhancing lesions compared to placebo at 6-, 12-, and 24-months ($p<0.001$) and fewer new or enlarged lesions of T2-weighted MRI scans at 24 months ($p<0.001$). Dose-related adverse events reported more frequently in fingolimod-treated patients than those receiving placebo included lower respiratory tract infections, bradycardia, atrioventricular conduction block, macular edema (1.25 mg group only), and elevated liver enzymes. The authors concluded that compared with placebo 0.5- and 1.25-mg daily doses of fingolimod significantly reduced annualized relapse rate, the risk of disability progression and MRI endpoints, and that adverse effects may be less common with the lower dose.

Cohen and associates performed a 1-year randomized, double-blind, double-dummy, active-controlled study called the **Tr**ial **A**ssessing Injectable **In**terferon versu**s** FTY720 **O**ral in **R**elapsing-Remitting **M**ultiple **S**clerosis (TRANSFORMS).[10] Prior therapy with interferon-beta or glatiramer acetate up to the time of randomization was permitted. Patients were randomized to receive oral fingolimod at a daily dose of 0.5- or 1.25-mg or intramuscular interferon beta-1a at a weekly dose of 30 mcg for up to 12 months. The primary endpoint was the annualized relapse rate. The main secondary endpoints included the number of new or newly enlarged T_2-weighted MRI scans at 12 months and disability progression that was sustained for at least 3 months. Neurological evaluations were performed at screening, every 3 months, and at the time of suspected relapses. The annualized relapse rate was significantly lower in patients treated with fingolimod 0.5 mg than in patients who received interferon beta-1a ($p<0.001$). The number of new and newly enlarging T2 lesions was significantly lower in patients treated with fingolimod than in patients who received interferon beta-1a ($p=0.002$). There was no significant difference in the time to 3-month confirmed disability progression between treatment groups at 1 year. Some adverse events reported more commonly in the fingolimod groups than the interferon beta-1a included herpes viral infection (1.25 mg group only), transient bradycardia, macular edema, and elevated liver enzymes. The authors concluded that oral fingolimod compared with intramuscular interferon beta-1a produced superior efficacy in reducing annualized relapse rate and MRI outcomes.

Adverse Reactions: The most common side effects associated with fingolimod 0.5 mg were headache, influenza, diarrhea, back pain, liver enzyme elevations and cough.[1] The only adverse event causing termination of therapy in clinical trials at an incidence of >1% was liver enzyme elevations. Serious side effects included bradyarrhythmia and atrioventricular blocks, infections, macular edema, respiratory and hepatic effects. Fingolimod was shown to induce a dose-dependent reduction in heart rate and has been associated with AV conduction delays including 1st or 2nd degree AV block following administration of the initial dose. Fingolimod may also cause a dose-dependent, reversible, reduction in the peripheral lymphocyte count to approximately 20-30% of baseline values. Before initiating treatment, a complete blood count within 6 months should be obtained. Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for VZV antibodies. It is recommended that antibody-negative patients receive VZV vaccine prior to initiation of fingolimod therapy. In clinical trials, macular edema occurred in 0.4% of patients who received fingolimod 0.5 mg, mostly in the first 3 to 4 months. Macular edema may resolve during treatment or after treatment discontinuation; however some patients may experience residual visual acuity loss even after resolution of macular edema. Furthermore, patients with diabetes mellitus and/or uveitis have an increased risk of macular edema and should have a baseline eye exam prior to initiation of therapy with scheduled follow-up ophthalmologic evaluations. Small dose-dependent reductions in forced expiratory volume over one second (FEV1) and diffusion capacity of the lung for carbon monoxide (DLCO) were observed in patients treated with fingolimod as early as 1 month after treatment initiation. Reductions in FEV1 appear to be reversible after treatment discontinuation; however, it is not known whether DLCO reductions are reversible upon discontinuation. Drug-related elevations in alanine aminotransferase can occur but may be transient with continued therapy or completely reversible upon discontinuation. It is recommended that baseline liver enzyme and bilirubin levels are determined at least 6 months prior to initiation of therapy.

Drug Interactions: Patients receiving concurrent therapy with Class Ia (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic drugs which increase the risk of torsades de pointes and those receiving medications which lower heart rate (e.g., atenolol, diltiazem) should be carefully monitored especially during initiation of therapy.[1] Ketoconazole may increase the blood levels of fingolimod and fingolimod-phosphate by 1.7-fold; patients on concurrent therapy should be closely monitored. Vaccines may be less effective in patients during and up to 2 months after discontinuation of fingolimod therapy. Due to the increased risk of infection, live attenuated vaccines should be avoided during and for 2 months after treatment is discontinued. Fingolimod should be used with caution in patients receiving other immunosuppressive or immunomodulating agents and in those being switched from long-acting immunosuppressive agents such as natalizumab (Tysabri®) or mitoxantrone (Novantrone®).

Pregnancy and Lactation: Fingolimod is classified as pregnancy-risk category C since there are no adequate well-controlled studies evaluating drug use in pregnant women.[1] A pregnancy registry is available and physicians are encouraged to register patients who become pregnant while exposed to fingolimod or within 2 months after stopping therapy. The telephone number for the fingolimod pregnancy registry is 1-877-598-7237. Additionally, fingolimod is excreted in the milk of treated rats, but it is unknown whether it is excreted in human milk. Any decision to discontinue either nursing or the drug should take into consideration the importance of drug therapy to the mother.

Dose and Administration: The recommended dose of fingolimod is 0.5 mg by mouth once daily.[1] The first dose of fingolimod should be given in a doctor's office or a clinic. Afterwards, the patient should be observed for signs and symptoms of bradycardia for 6 hours. A baseline electrocardiogram (ECG) should be obtained in those at higher risk of bradyarrhythmia or heart block (e.g., those receiving Class Ia or Class III antiarrhythmic drugs, beta blockers, calcium channel blockers, those with a low heart rate, history of syncope, sick sinus syndrome, 2nd degree or higher conduction block, ischemic heart disease, or congestive heart failure). If bradyarrhythmia-related symptoms occur after administration of the first dose, initiate appropriate management and continue observation until the symptoms resolve. There are no dosage adjustments for patients with renal and hepatic impairment. However, those patients with severe hepatic impairment should be closely monitored for adverse effects.

Risk Evaluation and Mitigation Strategy (REMS): The purpose of the fingolimod REMS is to inform patients and healthcare providers about the risks associated with fingolimod treatment.[11] The two elements of the fingolimod REMS include a medication guide and a communication plan. The medication guide is required to be dispensed with each fingolimod prescription and the communication plan includes two documents: "A Dear Healthcare Professional Letter" and a "Guide to Important Safety Information: Using Gilenya™ in Patients with Relapsing Forms of Multiple Sclerosis."

Cost and Formulary Status: Fingolimod is commercially available as a 0.5 mg capsule contained in 7-day and 28-day blister packs. Compared with other disease modifying agents for relapsing forms of MS, fingolimod is more expensive. For example, the average wholesale price (AWP) for month supply of Avonex® (interferon beta-1a) consisting of four 30-microgram vials is approximately $2,964, whereas the AWP for fingolimod is $158 per capsule which is approximately $4,742 per month.[12] Fingolimod is currently not on the Cleveland Clinic Health System Formulary.

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11. Risk Evaluation and Mitigation Strategy: Gilenya™ (fingolimod). Located at www.fda.gov. Accessed November 2010.
12. *Red Book: Pharmacy's Fundamental Reference*. Montvale, NJ: Thomson Healthcare; 2010:243.

Table 1. Comparison Between Commerically Available Products for Relapsing MS [1-8]

	MS Treatment Indication	Route of Administration	Dosage	Formulary Status
Fingolimod (Gilenya™)	Relapsing forms of MS	Oral	0.5 mg by mouth daily	No
IFN-β1a (Avonex®; Rebif®)	Relapsing forms of MS	IM, SC	Avonex® 30 mg IM once weekly Rebif® 44 mcg SC 3 times a week* Rebif® 22 mcg SC 3 times a week *	Yes
IFN-β1b (Betaseron®; Extavia®)	Relapsing forms of MS	SC	0.25 mg SC every other day*	No
Glatiramer acetate (Copaxone®)	Relapsing-remitting MS	SC	20 mg SC daily	No
Natalizumab (Tysabri®)	Relapsing forms of MS	IV	300 mg IV once a month	† Formulary restricted
Mitoxantrone (Novantrone®)	Secondary progressive, progressive relapsing, or worsening relapsing-remitting MS	IV	12 mg/m^2 every 3 months	Yes

MS = Multiple Sclerosis
IFN = Interferon
IM = Intramuscular
SC = Subcutaneous
IV = Intravenous

*Dose is titrated upward to this target dose
† Restricted to the Department of Neurology at the Mellen Center for the outpatient treatment of MS. Restricted to the Department of Gastroenterology for the treatment of Crohn's disease in outpatients failing to respond to other agents

Formulary Update

The CCHS Medical Staff P&T Committee met in October 2010, followed by the CC Local P&T Committee in November 2010, and the following decisions were made:

Additions:

1. **Cabazitaxel (Jevtana®)**: Cabazitaxel is indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen. It is **restricted** to the Department of Hematology/Oncology for use in the outpatient setting only.
2. **Buprenorphine/Naloxone (Suboxone®)**: Suboxone® is indicated as maintenance treatment for opioid dependence. The recommended maintenance target dose is 16 mg per day as a single daily dose (dosage should be adjusted in increments of 2 mg or 4 mg to a level which maintains treatment and suppresses opioid withdrawal symptoms and the usual range is 4 to 24 mg per day).
3. **Citocholine (CerAxon®):** Citocholine is classified as a dietary supplement by the Food and Drug Administration (this is an exception to the Cleveland Clinic Dietary Supplement Policy). Clinical indications for its use include neuroprotection after an ischemic stroke. Exogenous choline may preserve structural and functional integrity of the neuronal membrane. Adverse effects have been described as mild and infrequent. For acute ischemic stroke, the dose is 500 to 1000 mg orally twice daily. The optimal regimen would be 2000 mg a day for 42 days (short-term or acute treatment) and 1000 mg per day for long-term or chronic use. To date, there are no data suggesting reduced renal function or reduction in elimination in elderly population exists. CC Pharmacy will only be ordering a specific citocholine product (CerAxon® from Ferrer Pharmaceuticals) to ensure product quality and integrity. Citocholine is **restricted** to the Department of Neurology for the initiation of therapy; however, it may be continued by any prescriber if it is continuation of therapy from home.
4. **Tapentadol (Nucynta®):** Tapentadol is indicated for relief of moderate-to-severe acute pain. It is a tablet (50-, 75-, and 100-mg) and is a controlled-substance (CII). Tapentadol binds to μ-opiate receptors in the central nervous system causing inhibition of ascending pain pathways, altering the perception of and response to pain. It also inhibits the reuptake of norepinephrine, which modifies the ascending pain pathway. In clinical trials, tapentadol has been shown to be associated with less gastrointestinal disturbances compared to opioids. The recommended dosing is: For Day 1 50 to 100 mg every 4 to 6 hours as needed (may administer a second dose ≥ 1 hour after the initial dose and maximum dose on first day is 700 mg per day); For Day 2 and subsequent dosing, 50 to 100 mg every 4 to 6 hours as needed (maximum dose: 600 mg per day). It is more expensive compared to select opioids and tramadol. It is **restricted** for use in patients who have failed opioids due to gastrointestinal intolerance. In addition, if a patient has only mild-to-moderate pain, tramadol (Ultram®) should be recommended. Tapentadol will not be placed on any order sets within Epic.
5. **Prevnar 13® vaccine**: The manufacturer is discontinuing Prevnar 7 vaccine and is only manufacturing Prevnar 13®.

Change in Formulary Restriction:

1. **Nicardipine IV (Cardene® IV):** Expand restriction to include use by Pediatric Intensive Care Unit (PICU) for pediatric neurology patients as second-line therapy.

Deletion:

1. **Rosiglitazone (Avandia®):** Due to the safety issues and impending Risk Evaluation and Mitigation Strategy (REMS) requirements for rosiglitazone, it has been removed from the inpatient Formulary. It will be removed from all inpatient pharmacy areas. There will not be an automatic therapeutic interchange to pioglitazone (Actos®). An alternative alert screen will be placed in Epic educating the physicians about the removal of rosiglitazone from the Formulary.

Not Added to the Formulary:

1. **Valrubicin (Valstar®):** Valrubicin will not be ordered, stocked, or dispensed. It is a medication used for bladder cancer.
2. **Iloperidone (Fanapt®):** Iloperidone may be dispensed as continuation of therapy from home.
3. **Ecallantide (Kalbitor®):** Ecallantide will not be ordered, stocked, or dispensed. It is a medication used for the treatment of hereditary angioedema (HAE).