Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Generic Name: Fingolimod
PDL Class: Multiple Sclerosis Drugs
Preferred: Glatiramer (Copaxone), Interferon Beta-1a (Avonex), Interferon Beta-1a/Albumin (Avonex Administration Pack)
Non-Preferred: Mitoxantrone, Interferon Beta-1b (Betaseron), Natalizumab (Tysabri)

Brand Name (Manufacturer): Gilenya® (Novartis)
Comparator Therapies: Disease modifying treatments (Injectable)
Dossier received: Yes
Month/Year of Review: March 2012

EXECUTIVE SUMMARY:

FDA Approved Indications:[1] Fingolimod is a sphingosine 1- phosphate receptor modulator indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Background/Reason for Review: Fingolimod is the first oral agent approved by the FDA as a disease modifying treatment (DMT) for MS. Previously available DMT agents are only available as injections or infusions. These five injectable medications were reviewed in comparison with each other by the Oregon Health Resources Commission in May 2008. This monograph will evaluate the available evidence of safety, tolerability, efficacy, and other considerations to help determine fingolimod's role in therapy.

Issues/Key questions:

1) What is the comparative effectiveness of fingolimod and other disease-modifying treatments for MS?
2) Do fingolimod and other disease-modifying treatments for MS differ in harms?
3) Are there subgroups of patients based on demographics, socioeconomic status, other medications, severity of disease, or co-morbidities for which fingolimod is more effective or associated with fewer adverse events than other disease-modifying treatments?

Efficacy: Results of two phase 3 studies in patients with relapsing-remitting MS (RRMS) evaluated the efficacy and safety of fingolimod including one placebo-controlled 24-month trial (FREEDOMS) and a 12-month head-to-head trial with comparator interferon (IFN) beta-1a (TRANSFORMS).[2, 3] These trials included doses (1.25 mg daily) that are higher than the FDA approved dose of 0.5 mg once daily for treating RRMS. The FREEDOMS trial was a

randomized placebo-control trial comparing two doses of fingolimod (0.5 mg daily and 1.25 mg daily) with placebo. Both fingolimod doses showed a statistically significant difference compared to placebo in all measured outcomes in this study, including annualized relapse rate (0.18 vs. 0.4; RR 0.55, fingolimod 0.5 mg and IFN beta-1a, respectively) and disability progression (17.7% vs. 24.2%; RR 0.73).[2] There were no significant differences between the two fingolimod doses. In TRANSFORMS, fingolimod 0.5 mg and 1.25 mg were compared to treatment with intramuscular IFN beta 1-a 30 µg given weekly over 12 months. Fingolimod 0.5mg once daily and 1.25mg once daily resulted in lower annualized relapse rates compared to interferon beta-1a (0.16, 0.20, and 0.33 respectively; P<0.001) and resulted in more patients having no confirmed relapse at 1 year compared with interferon beta-1a (82.5%, 80.5%, and 70.1%; p<0.001; NNT 8.3 for fingolimod 0.5mg and NNT 10 for fingolimod 1.25mg). This study failed to show a significant difference in disability progression.[3] In a 12-month extension of this trial, patients who switched from interferon to fingolimod demonstrated a lower ARR after switching (fingolimod 0.5mg: 0.31 at year 1 vs. 0.22 at year 2; fingolimod 1.25mg 0.29 at year 1 vs. 0.18 at year 2).[4]

Safety: It was clear through the trials that higher doses lead to more frequent and more severe adverse events. The FDA has suggested that studies of lower doses, including 0.25 mg daily, be further evaluated. The most common adverse effects include influenza virus infections, headaches, diarrhea, and elevated liver enzymes. Macular edema occurred in 4 patients in the 1.25 fingolimod group (1%), 2 in the 0.5 mg group (0.5%), and none in the interferon group.[3] The risk of discontinuing drug due to an adverse event increased with fingolimod 1.25 mg once daily compared with fingolimod 0.5mg and with interferon beta-1a. After the first dose of fingolimod, 1.2% of patients taking 1.25mg, 0.6% taking 0.5mg experienced bradycardia, compared to 0.2% taking placebo and 0% taking interferon.[5] Due to the concern of bradycardia and atrioventricular block, patients must be observed for 6 hours after the initial dose.[1] The FDA released a safety announcement in December 2011 regarding a patient with MS who died within 24 hours of taking the first dose of fingolimod. At this time, the FDA cannot conclude whether the drug resulted in the patient's death and is continuing to evaluate the case.[6]

Conclusions:

- Based on only one head to head trial, there is low strength evidence that fingolimod results in lower annualized relapse rates than interferon beta-1a in patients with RMMS and that there is no difference in efficacy between the high or low dose of fingolimod (1.25mg vs. 0.5mg). There was no difference in disease progression.
- There is insufficient evidence to evaluate comparative effectiveness of fingolimod with any of the other disease modifying treatments approved for treatment of MS.
- The higher dose of fingolimod (1.25 mg) resulted in higher numbers and more severe adverse effects, as well as more patients discontinuing treatment.
- Further unanswered issues exist including:
    - Comparative effectiveness of fingolimod with different disease modifying treatments and of longer durations.
    - Further evaluation of safety concerns including the risk of macular edema, the effect of lung function, cancers, and serious viral infections. Fingolimod has a unique set of safety issues and a relatively small body of evidence to support long term safety
    - Applicability of these results to general MS population due to the narrow patient population included in study

Recommendations:

- Develop PA criteria to manage utilization of fingolimod and restrict use to neurologists, patients with RMMS, and ensure patients are not currently on therapy with an injectable DMT due to lack of safety and efficacy data.
- Consider requiring a failure to respond to a full and adequate course of interferon treatment.

BACKGROUND/CURRENT LANDSCAPE

MS is a chronic, autoimmune disease of the central nervous system affecting 2.1 million people worldwide and approximately 250,000 to 400,000 people in the United States.[8] The highest prevalence of MS occurs in Caucasian women who live in northern latitudes. In 2004, MS costs were estimated at $47,215 per patient per year, including 34% of these costs towards disease modifying drugs for treatment.[8] Four different clinical courses of MS have been defined and include relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive –relapsing MS (PRMS).[9] About 85% of patients have RRMS and most cases eventually develop into a SPMS.[5,8] The efficacy of fingolimod has been demonstrated in patients with RRMS. RRMS is the most common type of MS and rarely progresses between relapses, although the patient may never fully recover after a relapse.

The treatment of multiple sclerosis involves acute relapse treatment with corticosteroids, symptom management, and disease modification with disease-modifying drugs. The goal of disease-modifying drugs is to prevent relapses and progression of disability rather than treat individual symptoms or disease exacerbations.[8] Progression of disease is measured by the disability caused by MS and is commonly measured by the Expanded Disability Status Scale (EDSS) which is a scale from 0 (normal neurological examination) to 10 (death due to MS).

First-line drugs for the treatment of MS include interferon beta-1a (Avonex®), interferon beta-1b (Betaseron®), and glatiramer acetate (Copaxone®). These DMT's have shown positive safety profiles but have lower efficacy (approximately 30% reduction in annual relapse rate), compared to second-line treatments which have greater efficacy but many safety concerns. Second-line treatments include natalizumab (Tysabri®) and mitoxantrone (Novantrone®) and are generally used for patients who either did not respond or did not tolerate first-line injections. There are several clinical treatment guidelines for MS there is variability among the treatment guidelines and the principle and most comprehensive of them including from the American Academy of Neurology and the National Institute of Clinical Excellence are quite outdated (2002 and 2003).[10]

Subpopulations:[1,7]

Geriatrics*:* Clinical MS studies of GILENYA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. GILENYA should be used with caution in patients aged 65 years and over, reflecting the greater frequency of decreased hepatic, or renal, function and of concomitant disease or other drug therapy.

Pediatrics*:* The safety and effectiveness of GILENYA in pediatric patients with MS below the age of 18 have not been established.

Gender, race, ethnicity: Potential differences not evaluated due to differences in gender, race, or ethnicity.

CLINICAL PHARMACOLOGY[1,11]

Fingolimod is a structural analogue of endogenous sphingosine and undergoes phophyorlyation to produce finoglimod phosphate, the active moiety. Fingolimod targets MS through its effects on the immune system and involves reduction of lymphocyte migration into the central nervous system.

PHARMACOKINETICS[1,11]

Parameter	Result
Oral Bioavailability	93%
Cmax	12-16 hours
Protein Binding	99.7% protein bound (fingolimod and fingolimod-phosphate)
Elimination	After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are the major components in the feces with amounts of each representing less than 2.5% of the dose.
Half-Life	6-9 days
Metabolism	Fingolimod is primarily metabolized via human CYP4F2 with a minor contribution of CYP2D6, 2E1, 3A4, and 4F12.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints**:**

- Disability
- Clinical exacerbation/Relapse
- Withdrawals due to adverse effects
- Serious adverse events

Study Primary Endpoints:

- Annualized relapse rate (ARR)

Evidence Table

Ref./Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating; Comments
FREEDOMS [1]									
Kappos L, Radue EW, O'Connor P, et al RCT,DB, PC, Phase III	F1: Fingolimod 0.5mg QD F2: Fingolimod 1.25mg QD P: Placebo	Median age: 37.1 yrs Female: 69.9% With relapsing-remitting MS Median disease duration: 6.7 yrs Mean EDSS score: 2.4 #of relapses in previou year: 1.5; #of relapses in previous two yrs: 2.1; Approx. 59% of patients had no history of disease-modifying treatment Exclusion criteria: active infection, macular edema, diabetes, immune suppression, or clinically significant systemic disease	N= 1272 F1: 429 F2: 425 P:418	24 months	<u>Annualized relapse rate over 24 months</u>: F1: 0.18 (0.15 – 0.22) F2: 0.16 (0.13 – 0.19) P: 0.4 (0.34 – 0.47) P value: < 0.001 for both groups <u>Progression of Disability (%):</u> F1: 17.7% P: 24.2% RR 0.73 (0.56 to 0.95) P=0.02 F2: 16.6% P: 24.2% RR 0.68 (0.50-0.93) P=0.02 <u>Relapse free at 24 months :</u> F1: 70.4% (66.0 – 74.8) F2: 74.7% (70.4 – 78.9) P: 45.6% (40.7 – 50.6) HR vs. placebo: F1: 0.48 95% CI (0.39-0.61) p < 0.001 F2: 0.38 95% CI (0.3-0.48) p < 0.001	N/A ARR/NNT 6.6%/15 ARR/NNT 7.6%/13 ARR/NNT 24.8%/4 ARR/NNT 29.1%/3	<u>Withdrawals due to AE:</u> F1: 15 (3.5%) F2: 31 (7.2%) P: 24 (5.7%) <u>Total Withdrawals:</u> F1: 80 (18.8%) F2: 131 (30.5%) P: 115 (27.5%) RR 0.7 95% CI 0.5-0.9 (F1 vs P) P=0.002 RR 1.2 95% CI 0.9-1.4 (F2 vs P) P=0.3 <u>Any serious AE:</u> F1: 43 (10.1%) F2: 51 (11.9%) P: 56(13.4%)	NS N/A NS	Fair • More than 10% lost from time of randomization to study completion between groups • Although baseline characteristics of groups are similar, the adequacy of allocation and randomization is unclear • Safety analyses showed dose related toxicity, including bradycardia and AV block on the first dose, macular edema, LFTs increases and pulmonary toxicity Due to its MOA, there is potentia for increased risk of serious infections and neoplasms. The trial excluded pts with pre-existing DM, heart conduction disorders or pulmonary disease. To address the known ADES and to further evaluate serious ADEs, REMS is in place for post-market monitoring. • >10% overall attrition between groups

TRANSFORMS [2]									
Cohen JA, Barkhof F, Comi G, et al. RCT,DB, PC, PG Phase III	F1: Fingolimod 0.5mg QD F2: Fingolimod 1.25mg QD A: interferon beta-1a 30 µg weekly	Median age: 36.2 yrs Female: 67.3% Median disease duration: 5.9 yrs Mean EDSS score: 2.2 Approx. 49% had received prior interferon beta therapy; 14% received glatiramer acetate previously. Exclusions: Patients with a documented relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, immunosuppression (either drug- or disease-induced), clinically significant coexisting systemic disease	N= 1292 F1: 431 F2: 426 A: 435	12 months	<u>Annualized relapse rate (n/95% CI) :</u> F1: 0.16 (0.12-0.21) F2: 0.20 (0.16- 0.26) A: 0.33 (0.26-0.42) P<0.001 (F1 vs. A and F2 vs. A) *Pts who had no previous disease-modify therapy:* F1: 0.15 (0.10-0.23) F2: 0.17 (0.11-0.25) A: 0.31 (0.22-0.41) *Pts who had previous disease-modify therapy:* F1: 0.26 (0.19– 0.34) F2: 0.33 (0.26 -0.42) A: 0.53 (0.43 – 0.65) <u>Patients with no disability progression(%) :</u> F1: 94.1 (91.8 – 96.3) F2: 93.3 (90.9 – 95.8) A: 92.1 (89.4 – 94.7) P=0.25 (F1 vs. INF) P=0.5 (F2 vs. INF) <u>Relapse free /95% CI:</u> F1: 354 (82.5%) (79.0 – 86.3) F2: 338 (80.5%) (75.9 – 83.7) A: 302 (70.1%) (64.8 – 73.8) RR 1.2 95% CI 1.1-1.3 (F1 vs. IFN) RR 1.1 95% CI 1.0-1.2 (F2 vs. IFN) P<0.001 (both groups vs. IFN)	N/A NS NS NS <u>ARR:</u> F1: 12.4% F2: 10.4% <u>NNT:</u> F1: 8.3 F2:10	<u>Withdrawals due to adverse events:</u> F1: 16 (3.7%) F2: 32 (7.6%) A: 12 (2.8%) RR 2.7 95% CI (1.3-5.5): F2 vs A P=0.002 <u>Total Withdrawals:</u> F1: 62 (14.8%) F2: 44(10.3%) A: 51 (11.8%) <u>Any serious event:</u> F1: 30 (7.0%) F2: 45(10.7%) A: 25 (5.8%)	ARI/NNT: 4.8%/21 (NS for F1) NS	Fair. • Around 50% of patients in trial had used interferon prior to enrollment. Despite the double dummy design, patients with prior experience with interferon may have more likely to have guessed which treatment they were on, due to previous experience with ADEs. • The success of blinding patients or neurologist was not evaluated • The rates of progression reported in this trial were much lower those found previous disease modifying drugs trials where beta interferon groups at years ranged from 11.4% to 26.6% and in placebo groups from 20.3% to 36.4%[3]. • Unclear if randomization metho adequate • >10% overall attrition

TRANSFORMS Extension Study [4]									
Khatri B, Barkhof F, Comi G, et al. RCT,DB, PC, PG	F1: Fingolimod 0.5mg QD F2: Fingolimod 1.25mg QD F1N: Fingolimod 0.5mg QD F2N: Fingolimod 1.25mg QD *F1N and F2N are patients who recv'd interferon beta-1a in TRANSFORMS study.	1027 patients in TRANSFORMS study entered additional 12 months extension study. All patients who completed the core TRANSFORMS study were eligible for extension	N= 1027 F1: 356 F2: 330 F1N: 167 F2N: 174	12 months	<u>Annualized relapse rate 95% CI(1</u> <u>end point) :</u> 0-12 months: F1: 0.12 (0.08-0.17) F2: 0.15 (0.1-0.21) F1N: 0.31 (0.22-0.43) F2N: 0.29 (0.20– 0.40) 13-24 months: F1: 0.11 (0.08-0.16); p* = 0.8 F2: 0.11 (0.08– 0.16); p=0.12 F1N: 0.22 (0.15-0.31); p=0.049 F2N: 0.18 (0.12-0.27); p=0.024 *p-value months 13-24 versus months 0-12	<u>ARR:</u> F1N: 0.01 F2N: 0.04 <u>NNT:</u> F1N:100 F2N:25	<u>Discontinuations Due to adverse effects:</u> F1: 9 (2.5%) F2: 11 (3.3%) F1N: 6(3.6%) F2N: 11 (6.3%) <u>Infectious events:</u> F1N (0-12mo): 97 (58%) F1N (13-24): 91 (54%) F2N (0-12): 88 (51%) F2N (13-24): 91 (52%) <u>Any serious AE:</u> F1N (0-12mo): 10 (6%) F1N (13-24): 8 (5%) F2N (0-12): 8 (5%) F2N (13-24): 21 (12%)	NA	Poor • Patient and investigators blindin was lost due to study design. • Norvatis collected and analyzed the data. • The study authors acknowledge the extension study has no placebo or active comparator group. The benefits after the switching cannot conclusively shown to be solely due to fingolimod. This also applies to risks associated with fingolimod. • Authors also noted the conclusions of study are based o a large number of analyses without adjustment for multiple comparisons. • Patients who withdrew from the TRANSFORMS study did not ente extension study, the findings of this study should be interpreted cautiously. • Overall rate of attrition of 15%

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Clinical Findings –

The FREEDOMS trial was a 2-year, double-blind Phase II study. The primary endpoint was the annualized relapse rate and the secondary endpoint was the time to disability progression. The ARR was 0.18 in the fingolimod 0.5mg, 0.16 in the 1.25 mg fingolimod group, and 0.40 in the placebo group ($p<0.001$ for both doses versus placebo).[2] Both treatment experienced and treatment naïve patients demonstrated significant reductions in annual relapse rate. Fingolimod reduced the risk of disability progression, confirmed after 3 months, over the 24-month study period (hazard ratios [HR], 0.70 for fingolimod 0.5 mg and 0.68 for fingolimod 1.25 mg).[2]

The TRANSFORMS trial evaluated two strengths of fingolimod to an active comparator, interferon beta-1a (Avonex). The most recent systematic review conducted by the Oregon EPC Drug Effectiveness Review Project (DERP) concluded that there was fair evidence that interferon beta-1a (Avonex) is less effective than interferon beta 1a SC (Rebif) and interferon beta-1b (Betaseron) in preventing in patients with RRMS, and that there is few differences in effectiveness or direct evidence is lacking for other outcomes.[7] The TRANSFORMS trial was large, relative to other trials of drugs to treat MS, enrolling 1292 patients.[3,5] The ARR was significantly lower in both groups receiving fingolimod (0.2 in the 1.25mg group, 0.16 in the 0.5mg group, 0.33 in the IFN-B1a group; $p<0.001$).[3] Other measures of relapse also showed both fingolimod doses to be superior. However, the numbers needed to treat for the proportion relapse-free with fingolimod compared with interferon beta-1a at 1 year were not very small (8.3 and 10).[5] Disability progression was not different significantly between fingolimod and interferon beta-1a . The benefit of fingolimod over interferon beta-1a was greater in the subgroup of patients who had prior exposure to a DMT (difference in 0.20 to 0.27 relapses) than in patients who had no exposure (0.13 to 0.16 relapses). A post hoc analysis of the TRANSFORMS trial showed that the rate of outpatient steroid use was higher in the interferon group (11.2%, 13.1%, and 18.3% for fingolimod 0.5 mg, 1.25mg, and IFN beta-1a respectively) and the rate of hospitalization was lowest in the 0.5mg fingolimod group and highest in the interferon group (1.9% vs. 7%; $p=0.001$).[5] In the TRANSFORMS trial, two fatal infections occurred. The most common adverse reactions to treatment with fingolimod include influenza virus infections, headaches, diarrhea and elevated liver enzyme activity. Higher rates of pyrexia (RR 4.26), influenza-like illness (RR 10.55), were found with interferon beta-1a, while a higher rate of increased alanine aminotransferase (RR 3.52) was found with fingolimod.[5] Other measures of relapse (relapse-free, proportion with multiple relapses, and the time to first relapse) also showed fingolimod doses to be superior but progression of disease was not different between the treatments after one year. The benefit of fingolimod over interferon beta-1a was greater in the subgroup of patients who had prior exposure to a disease-modifying drug than in patients who had no prior exposure, although not statistically significant. Overall, there were no differences in the rate of discontinuation over 1 year, including for both lack of efficacy and due to adverse events.

In the TRANSFORMS 12-month extension trial, patients originally assigned to receive fingolimod in the TRANSFORMS study continued, and patients receiving interferon were re-randomized to receive fingolimod 0.5 mg or 1.25 mg.[4] This extension study lost the inherent placebo or active comparator control group when switching patients and all patients were aware that they were receiving fingolimod making it essentially open-label. Therefore, it is difficult to draw conclusions from the analysis. Patient's who withdrew from the core TRANSFORMS study were also excluded from this analysis. Patients who received interferon beta-1a in the core study (months 1-12) had relative reductions in ARR during months 13-24 of 30% after switching to 0.5mg fingolimod (ARR ratio 0.7, 95% CI 0.49-1.00, $p=0.49$) and 36% after switching to 1.25mg (0.64, 95% CI 0.43-0.94, $p=0.024$).[4]

There was also a small (n=277) placebo-controlled trial that only last 6 months that used MRI findings as the primary outcome, and the clinical relevance is uncertain. In addition, this trial used doses higher than was ultimately approved by the US FDA (5mg once daily and 1.25 mg once daily). Therefore this study was not included in our evidence table or critical appraisal process.[5,12]

DRUG SAFETY[1]

Serious: No absolute contraindications have been determined.

Warnings:

- Bradyarrhythmia and Atrioventricular Blocks: All patients should be observed for 6 hours after the first dose for signs and symptoms of bradycardia.
- Increased risk of infections due to a dose dependent reduction in peripheral lymphocyte count
- Macular edema
- Elevations in liver enzymes

Tolerability: In the FREEDOMS trial 14.2% of patients in the 1.25 mg fingolimod group, 7.5% in the 0.5 mg fingolimod group, and 7.7% in the placebo group discontinued therapy. Major reasons included bradycardia, macular edema, elevated liver enzymes, and mild hypertension. In the TRANSFORMS trial 10% of patients receiving fingolimod 1.25 mg, 5.6% receiving fingolimod 0.5 mg, and 3.7% receiving interferon beta 1a discontinued study treatment. Main adverse events due to discontinuation included bradycardia and atrioventricular block after the first dose.

Pregnancy/Lactation rating: Pregnancy Category C

Dose Index (efficacy/toxic): No cases of overdosage have been reported. However, single doses up to 80-fold the recommended dose (0.5 mg) resulted in no clinically significant adverse reactions. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

Look-alike / Sound-alike (LA/SA) Error Risk Potential

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
Fingolimod	None	None	None	None	None
Gilenya	None	None	None	None	Glatiramer Injection

Common Drug-Related Adverse Events [1]		
Adverse Events (%)	**Fingolimod 0.5 mg daily (%)**	**Placebo (%)**
Number of Patients	425	418
Infections		
Influenza Viral Infections	13	10
Herpes Viral Infections	9	8
Bronchitis	8	4
Sinusitis	7	5
Cardiovascular Disorders		
Bradycardia	4	1
Abdominal Pain		
Macular edema	0.7	0
Gastrointestinal		
Diarrhea	12	7
Laboratory Tests		
ALT/AST increased	14	5
Increased blood triglycerides	3	1
Musculoskeletal Disorders		
Back pain	12	7
Nervous System Disorders		
Headache	25	23
Dizziness	7	6
Paresthesia	5	4
Migraine	5	1
Psychiatric Disorders		
Depression	8	7
Skin and Subcutaneous Tissue Disorders		
Alopecia	4	2
Pruritis	3	1

DOSE & AVAILABILITY[1]**:**

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
0.5 mg	Tab	PO	Daily	The blood level of some metabolites is increased in severe renal impairment. The toxicity of these metabolites has not been explored.	Patients with severe hepatic impairment should be monitored for adverse reactions.	Safety and effectiveness have not been established	GILENYA should be used with caution in patients aged 65 years and over, reflecting the greater frequency of decreased hepatic, or renal, function and of concomitant disease or other drug therapy.	With or without food. Patients should be observed for 6 hours after the initial dose to monitor for signs and symptoms of bradycardia.

ALLERGIES/INTERACTIONS[1]

Drug-Drug: Ketoconazole can increase fingolimod blood levels by 1.7-fold when coadministered. The risk of adverse effects may be increased.

Heart rate lowering drugs: Experience with GILENYA in patients receiving concurrent therapy with beta blockers is limited. These patients should be carefully monitored during initiation of therapy.

Vaccines: Vaccination can be less effective during and for up to 2 months after discontinuation of treatment with fingolimod.

REFERENCES

1. Gilenya. Prescribing Information. Novartis Pharmaceuticals Corp; Available at: http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf.

2. Kappos L, Radue E-W, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* 2010;362(5):387-401.

3. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* 2010;362(5):402-415.

4. Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. *Lancet Neurol*. 2011;10(6):520-529.

5. McDonagh M. Disease-modifying drugs for multiple sclerosis: Single drug addendum: Fingolimod. Final original report. Available at: http://derp.ohsu.edu/about/final-document-display.cfm. Accessed January 30, 2012.

6. Commissioner O of the. Safety Alerts for Human Medical Products - Gilenya (fingolimod): Drug Safety Communication - Safety Review of a Reported Death After the First Dose. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm284355.htm. Accessed January 30, 2012.

7. Smith B, Carson S, Fu R, et al. Drug Class Review: Disease-modifying Drugs for Multiple Sclerosis. Update 1. Available at: http://derp.ohsu.edu/about/final-products.cfm. Accessed January 24, 2012.

8. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):169-178.

9. Miller RM, Happe LE, Meyer KL, Spear RJ. Approaches to the management of agents used for the treatment of multiple sclerosis: consensus statements from a panel of u.s. Managed care pharmacists and physicians. *J Manag Care Pharm*. 2012;18(1):54-62.

10. Center for Drug Evaluation and Research. Application Number: 22-527. Summary Review.

11. David OJ, Kovarik JM, Schmouder RL. Clinical pharmacokinetics of fingolimod. *Clin Pharmacokinet*. 2012;51(1):15-28.

12. Kappos L, Antel J, Comi G, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N. Engl. J. Med.* 2006;355(11):1124-1140.

13. Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf.

Appendix 1:

Strength of Evidence Grades and Definitions Used[13]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

Methods to assess quality of trials[13]

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.
5. Were outcome assessors blinded to treatment allocation?	

6. Was the care provider blinded? **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition