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APPLICATION NUMBER:

22-527

SUMMARY REVIEW

MEMORANDUM

DATE: September 19, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-527

SUBJECT: Recommendation for Action on NDA 22-527, for the use of Gilenya (fingolimod) in the treatment of adults with relapsing forms of Multiple Sclerosis (MS)

NDA 22-527, for the use of Gilenya (fingolimod) in the treatment of adults with relapsing forms of Multiple Sclerosis (MS), was submitted by Novartis Pharmaceuticals Corporation on 12/18/09. Gilenya is an oral sphingosine-1-phosphate (S1P) modulator whose mechanism of action presumably relates to its ability to bind to S1P receptors on various lymphocytes, preventing their egress out of lymphoid tissue into the peripheral circulation and thereby into the Central Nervous System (CNS) with a resulting decrease in inflammatory response. Fingolimod itself is inactive, but is phosphorylated to the active moiety, fingolimod-P.

The sponsor has submitted the results of two definitive controlled trials that purport to provide substantial evidence of effectiveness as well as safety data and the requisite other data adequate for review. Because Gilenya is the first NDA for an oral treatment for MS to be submitted, it was granted Fast Track status and was given a priority review designation. The application was discussed at a meeting of the Peripheral and Central Nervous Systems Advisory Committee (PCNS AC) on 6/10/10.

The application has been reviewed by Dr. Heather Fitter, medical officer, Dr. Sharon Yan, statistician, Dr. Lourdes Villalba, safety reviewer, Dr. Sally Yasuda, safety team leader, Drs. Ju-Ping Lai and Jagan Parapelly, clinical pharmacologists, Dr. Richard Siarey, pharmacologist, Dr. Lois Freed, supervisory pharmacologist, Dr. Wendy Wilson, chemist, Dr. Gwynn Ison, Division of Oncology Products, Dr. Marc Cavaille-Coll, Division of Special Pathogen and Transplant Products, Dr. John Senior, Office of Surveillance and Epidemiology (OSE), Dr. Shari Targum, Division of Cardiovascular and Renal Products, Dr. Wiley Chambers, Division of Ophthalmology Products, Dr. Brian Porter, Division of Pulmonary, Allergy, and Rheumatology Products, Felicia Duffy and Dr. Denise Baugh, Division of Medication Error Prevention and Analysis, Dr. Quynh-Van Tran, Division of Drug Marketing, Advertising, and Communications, Dr. Antoine El-Hage, Division of Scientific Investigations, Dr. Alicja Lerner, Controlled Substance Staff, Drs. Yasmine Choudhry and Marcia Britt, Office of Surveillance and Epidemiology, and Dr. Eric Bastings, Deputy Director and Cross-Discipline

Team Leader (CDTL), DNP. The review team (with the exception of Dr. Siarey), recommends that the application be approved, albeit with numerous post-marketing requirements and commitments.

Dr. Bastings's CDTL memo provides a detailed review of the relevant effectiveness and safety data, and I will not repeat all of the details here. I will very briefly summarize the relevant data, and offer the rationale for the division's recommendations.

Clinical Pharmacology

As noted above, fingolimod is phosphorylated to the active S-enantiomer fingolimod-P. Fingolimod-P reaches Tmax at about 6 hours; the Tmax for fingolimod is about 12 hours. Fingolimod and fingolimod-P each have a T1/2 of about 6-9 days, and steady state is achieved in about 1-2 months.

In addition to being phosphorylated, fingolimod is metabolized by CYP 4F2, and non-polar ceramide analogs of fingolimod are also formed. After single doses, fingolimod represents about 23% of circulating moieties, with fingolimod-P representing about 10%, with numerous other metabolites (presumably inactive) at lesser concentrations.

Fingolimod and fingolimod-P are not excreted in the urine, but about 81% of a dose is excreted in the urine as inactive metabolites.

Effectiveness

Briefly, as noted above, the sponsor has submitted the results of two randomized controlled trials. Study 2301 was a two year randomized trial in which 1272 patients with Relapsing-Remitting MS (RRMS) were randomized to receive fingolimod 0.5 mg/day, 1.25 mg/day, or placebo. Study 2302 was a one year study in which 1292 patients with RRMS were randomized to either fingolimod 0.5 mg/day, 1.25 mg/day, or Avonex (interferon beta-1a), 30 mcg once weekly (this study utilized "double dummy" blinding). Each study examined the effects of fingolimod on the annualized relapse rate (ARR) and on disease progression, as defined by time to confirmed (i.e., confirmed persistent change at 3 months) progression on the Expanded Disability Severity Scale (EDSS; progression defined as a 1 point change if the baseline EDSS was less than 5.5, and a 0.5 point change otherwise).

In each study, patients receiving fingolimod had a statistically significant benefit on the primary outcome (annualized relapse rate; ARR) compared to control. The following table presents these results:

	Adjusted ARR	P-value vs control

Study 2301

Fingolimod 1.25	0.16	<0.001
Fingolimod 0.5	0.18	<0.001
Placebo	0.40	

Study 2302

Fingolimod 1.25	0.20	<0.001
Fingolimod 0.5	0.16	<0.001
Avonex	0.33	

Time to confirmed relapse was significantly delayed for both fingolimod groups compared to placebo in Study 2301 (p-values 0.012 and 0.026 for fingolimod 1.25 mg and 0.5 mg, respectively; the percentage of patients without progression at Month 24 was 85%, 83%, and 78% for fingolimod 1.25, 0.5, and placebo, respectively, with p-values of 0.008 and 0.043, respectively).

In Study 2302, there were no statistically significant differences on time to confirmed disability among any of the groups. The number of patients who progressed at Month 12 was 10.3%, 10.1%, and 14.1% in the fingolimod 1.25 mg, 0.5 mg, and Avonex groups, respectively. The mean change in the baseline score of EDSS was -0.1, -0.8, and 0.2 in the fingolimod 1.25, 0.5, and Avonex groups, respectively (the 1.25-Avonex comparison was nominally significant with p-value 0.04).

The sponsor also assessed the number of new or newly enlarged Ts lesions on MRI at study end. The following table gives the results for both studies:

Study 2301

	Mean # of new or newly enlarged T2 lesions	P-value
Fingolimod 1.25	2.5	<0.001
Fingolimod 0.5	2.5	<0.001
Placebo	9.8	

Study 2302

Fingolimod 1.25	2.5	0.02

Fingolimod 0.5	3.5	0.05
Avonex	4.9	

Pharmacokinetic-pharmacodynamic (PK/PD) modeling suggests that a dose of 0.25 mg/day would be effective, albeit at a level somewhat less than that achieved with the 0.5 mg/day dose.

Safety

Fingolimod has been studied in 2615 patients at a dose of 0.5 mg/day or greater, with 1843 exposed for at least one year, and 1224 exposed for at least two years.

Fingolimod has been studied in renal-transplant patients at doses up to 5 mg/day, and at those doses is associated with numerous significant adverse events, including cardiac, respiratory, and ophthalmic. The Agency's detailed safety review has concentrated on an assessment of the experience at the (b) (4) doses for MS, namely 0.5 and 1.25 mg/day.

As discussed by the review team, there were 14 deaths in the MS program, one in a patient receiving 0.5 mg/day (8 occurred in patients receiving 1.25 mg/day). The death in the patient receiving 0.5 mg/day occurred 1 year after drug discontinuation. An autopsy revealed diffuse B cell lymphoma of the brain (Epstein-Barr associated), and, according to Dr. Yasuda, accompanying "non-methotrexate-associated iatrogenic immunodeficiency associated lymphoproliferative disorder" of the lung, kidney, thyroid, jejunum, and T cell lymphoma of the skin. Several deaths in the 1.25 mg dose group were considered likely related to treatment (2 cases of herpes infections), or possibly related (2 cases of unusual MS progression and 2 metastatic tumors.

In the MS experience, there was, in general, a low rate of serious adverse events including the following:

Event	1.25	0.5	Placebo
	N=943	N=854	N=511
Bradycardia	1.6	0.7	0.2
First degree AV block	0.4	0.1	0
Second degree AV block	0.4	0.1	0.2
Herpes infection	0.4	0.2	0
LFT abnormality	0.7	0.5	0.2
Macular Edema	0.4	0.1	0

Lymphopenia	0.3	0	0

The following events led to discontinuation (taken from Dr. Bastings's Table 9, page 15 of his memo):

Event	1.25	0.5	Placebo
	N=943	N=854	N=511
LFT abnormalities	4.1	3.4	1.4
Macular edema	1.1	0.1	0
Bradycardia	0.5	0	0.2
First degree AV block	0.3	0	0
Second degree AV block	0.2	0	0

Common adverse events are discussed by Dr. Bastings (page 16 of his memo); they are consistent with the events described as serious and are of no additional significance.

Laboratory data

Fingolimod causes a peripheral lymphopenia, consistent with its primary pharmacologic action. Lymphocyte counts drop to about 28% of baseline at 0.5 mg daily (about 23% of baseline at 1.25 mg daily) and persist during treatment. In general, levels essentially return to baseline within 3 months of discontinuation of treatment. In about 20% of patients, the nadir of lymphocyte counts was about 10% of baseline.

Systematic collection of routine electrolytes was not performed in the Phase 2 and 3 MS studies.

Fingolimod causes changes in blood pressure. After the initial dose, there is an acute hypotensive effect, followed by a hypertensive effect with chronic treatment, as described in the following tables:

Acute dosing

BP Changes

SBP < 90 or >20 mm decrease From baseline	DBP < 50 or >15 mm decrease from baseline

Fing 1.25	23%	29%
Fing 0.5	19%	23%
Placebo	16%	17%

Bradycardia

	<50 bpm or >15 bpm decrease From baseline
Fing 1.25	48%
Fing 0.5	33%
Placebo	13%

Chronic dosing

	20 mm Hg Increase In SBP	>15 mm Hg increase in DBP
Fing 1.25	27%	25%
Fing 0.5	22%	22%
Placebo	20%	20%

There were small dose dependent increases in mean blood pressure (systolic and diastolic) that peaked at about 6 months and continued during treatment (see Dr. Bastings's Table 13, page 18 of his memo). There were also small dose dependent increases in the percentage of patients who met outlier criteria for both SBP and DBP (see Dr. Bastings's Table 15, page 19).

Issues of interest

Bradycardia and AV block

Fingolimod causes significant bradycardia at all doses, including at 0.5 mg, apparent after the first dose, reaching a nadir at about 5-6 hours, as described earlier. With continued daily treatment, the heart rate essentially returns to baseline in about 1 month. Although there were a few serious AEs and discontinuations related to cardiac reasons (most commonly bradycardia, followed by second and first degree AV block), almost all occurred in the 1.25 mg group; only one patient discontinued in the 0.5 mg group for a cardiac reason.

Patients in studies 2301 and 2302 were monitored for 6 hours (at least) for cardiac events; 18%, 12%, and 3% of fingolimod 1.25 mg, 0.5 mg, and placebo required more extended monitoring because of persistent effects. A total of 2%

of fingolimod 0.5 mg patients required observation in the hospital, compared to 0% of the placebo patients.

Because of cardiac lesions seen in animal studies, some patients were assessed with echocardiography. Although the assessments were limited, Dr. Targum, cardiology consultant, concluded that there were no significant findings.

Macular edema

Because macular edema was noted in studies of renal transplant patients (at higher doses the rate was about 4%), patients in the MS studies were monitored for macular edema with periodic Optical Coherence Tomography (OCT). There were 4 serious cases of macular edema in the 1.25 mg group and 1 serious case (0.1%) in the 0.5 mg group. These all led to discontinuation of treatment. In all studies combined, there were 0.2% serious cases in the 0.5 mg group.

In MS controlled trials, the DSMB ophthalmologist diagnosed ME in 0.8%, 0.9%, and 0.3% in fingolimod 1.25 mg. 0.5 mg, and placebo patients, respectively.

There were very few differences on OCT between the 0.5 mg group and the placebo group. Most cases of ME were diagnosed on testing, and were asymptomatic. The median time to detection was 99 days, with a mean time to detection of 207 days. Dr. Chambers, ophthalmology consultant, concluded that there were only a small number of cases of ME in the 0.5 mg group, and that they were reversible upon discontinuation of treatment.

Pulmonary changes

Based on animal findings of pulmonary fibrosis and hypertrophy of the smooth muscle as well as findings of dyspnea and pulmonary edema in the renal transplant experience, patients in MS trials were monitored with High Resolution CT scans (HRCT) in a subset of patients, and pulmonary function tests (FEV1, FVC and carbon monoxide diffusing capacity [DLCO]).

As described by Dr. Bastings (Figures 4, 5, and 7 in his memo, pages 26-7), there were dose dependent decrements in all of these measures. Specifically, there was an initial drop (about a 0.1 L/sec decrement at the 0.5 mg dose in FEV1 that remained abnormal but did not further deteriorate; about a 0.25 mL/min/mmHg change in DLCO that increased to about a 1 mL/min/mmHg change at month 12, and then approached baseline at month 24; it should be noted that for DLCO, there were considerably fewer patients assessed at later time points compared to earlier time points). A greater percentage of patients in the 0.5 mg group had a DLCO <80% of baseline compared to placebo (16% vs 12%, respectively). Although FEV1 changes resolved with drug discontinuation, this was not true for DLCO changes. These changes did not correlate with any

pulmonary symptoms. There were no material differences between the results at the 0.5 mg group and placebo on HRCT or FVC.

Liver abnormalities

Fingolimod causes an increase in liver enzymes.

In controlled MS trials, there was a 10%, 9%, and 2% incidence in the percent of patients who experienced an increase of at least 3 XULN in ALT in the fingolimod 1.25 mg, 0.5 mg, and placebo groups, respectively. The corresponding percentages for AST were 1.5%, 2%, and 1%. For GGT, the corresponding percentages were 9%, 7%, and 1%. The incidence of ALT or AST increases of >5 XULN were much less, and minimally different from placebo. For GGT, the percentages of patients with elevations >5 X ULN were 3%, 2%, and 0%. There were no important changes in bilirubin. There was one patient with an ALT elevation and jaundice who was diagnosed with Hepatitis E.

Non-clinical issues

As noted above, Dr. Siarey, the reviewing pharmacologist, has recommended that the application not be approved at this time. As described by Dr. Freed, his reasons are:

1) reproductive and developmental studies are inadequate because of a lack of fetal assessment at all doses
2) in the in vitro genetox studies, there is inadequate information on the amount of phosphorylated fingolimod formed by the metabolic activation system used
3) the mouse carcinogenicity study was inadequate because of a high reported rate of autolysis, and
4) the safety of metabolites M2 and M3, which are markedly elevated in patients with severe renal impairment, have not been adequately assessed

Dr. Freed has, in my view, adequately dealt with these issues in her memo.

Briefly, with regard to the first issue, there were inadequate numbers of mid dose females (MDF) in the fertility study and there was no assessment of skeletal abnormalities in the low dose (LD) and mid-dose (MD) embryo-fetal development study in the rat. According to Dr. Freed, however, the latter concern is mitigated by the fact that there were no abnormalities seen at the high dose (HD). The former concern is mitigated by the fact that there were adequate numbers of high dose females (HDF).

Regarding the second issue, Dr. Freed agrees that the genetox battery was inadequate (for reasons beyond those cited by Dr. Siarey, although she agrees with his reason as well). However, as she notes, the carcinogenicity studies clearly demonstrate a signal for malignant lymphomas (see below), so no additional genetox studies are necessary.

Regarding the issue of the adequacy of the mouse carcinogenicity study, Dr. Freed concludes that autolysis did not materially interfere with the adequate assessment of neoplastic findings (indeed, there were positive findings). Although this may have interfered with the assessment of non-neoplastic findings, as she points out, this is not the purpose of a carcinogenicity study.

Finally, regarding the assessment of the toxicity of M2 and M3, Dr. Freed notes that levels of M2 and M3 have been adequately assessed except in the pre-and post-natal development study and the carcinogenicity studies. However, as she notes, the levels of M2 and M3 in the mouse carcinogenicity study were likely to have been "…at least similar…" to those seen in patients with severe renal impairment. For this reason, she believes that no additional non-clinical studies need be done to evaluate these metabolites.

As noted earlier, fingolimod causes lung pathology, but the primary finding of importance not detectable in the clinical studies to date is a dose-related increase in malignant lymphomas in MD and HD male and female mice (0.25 and 2.5 mg/kg/day).

Risk Evaluation and Mitigation Strategies (REMS)

Because of the various adverse events associated with the use of fingolimod, the sponsor has proposed a REMS consisting of a Medication Guide, a Dear Health Care Practitioner letter, and an information sheet to be given to prescribers.

Comments

The sponsor has submitted the results of two randomized controlled trials that purport to establish substantial evidence that GILENYA is effective in reducing relapses and delaying the accumulation of disability in adults with RRMS. Further, the sponsor has submitted detailed reports of relevant safety data as well as other required data.

As noted above, due to the panoply of adverse events caused by fingolimod, the application was discussed at a meeting of the PCNS AC on June 10, 2010. Following is a brief account of the responses to the questions we asked the committee to consider.

1) The committee voted unanimously that there was substantial evidence of effectiveness for fingolimod in reducing the incidence of relapses in patients with RRMS, and voted 24-1 that there was substantial evidence of effectiveness inn delaying the accumulation of physical disability in these patients.

2) The committee voted 20-5 that the sponsor should be required to evaluate the effectiveness of doses lower than 0.5 mg/day, and unanimously that this could be done post-approval.

3) The committee voted unanimously that the safety data for 0.5 mg daily justified approval, and also voted unanimously that patients should receive the first dose in a monitored setting. Most members recommended that this be true for all patients, but the cardiologists felt that only patients at high risk for arrhythmias/bradycardia be monitored.

4) The committee voted 20-4 (one abstention) that routine ophthalmologic monitoring was not sufficient to detect ME, and, in discussion, most members felt that a baseline exam, including dilated fundoscopy, be performed.

5) The committee voted 17-7 (one abstention) that routine vigilance was insufficient to mitigate the pulmonary risk, and the committee's pulmonology consultant felt that patients should have baseline PFTs.

6) The sponsor had proposed a 5 year, 5000 patient post-marketing study of the 0.5 mg dose in routine care, to further assess its adverse effects, especially in populations excluded from the MS studies (e.g., diabetes, cardiovascular disease). The committee agreed that such assessments should be performed.

7) The committee voted 21-3 (one abstention) that fingolimod should not be reserved for patients intolerant of, or who have had an inadequate response to, other available MS treatments.

We agree that the sponsor has provided substantial evidence of effectiveness for GILENYA as a treatment for relapses in patients with RRMS. Further, although they have submitted only one study (2301) that demonstrates a significant effect on the accumulation of disability, we also agree that it is appropriate to grant this claim. The lack of a significant effect on this outcome in Study 2302 is not unexpected: In this study, fingolimod was not compared to placebo, and the study was only one year in duration. The very robust finding on relapse rate in both studies (including compared to an active control), as well as the robust finding on disability in Study 2301 make granting the disability claim appropriate, in our view.

Further, we believe it is appropriate to grant these claims for patients with relapsing forms of MS, not just for patients with relapsing-remitting MS.

Relapsing forms of MS are those in which patients do not recover completely between relapses, and these are, in general, patients who have more severe disease. In these two studies, the drug clearly had an effect on patients with high EDSS scores (i.e., more severe patients) as well as in those with lower scores. We believe that this finding makes it reasonable to conclude that the drug is effective in reducing relapses and accumulated disability in patients with other relapsing forms of MS in addition to RRMS (also, it is worth noting that the other approved treatments carry this expanded indication).

It is important to note that there were no important differences between the effectiveness at 0.5 mg/day and 1.25 mg/day, and that significant adverse events were dose related. For these reasons, we believe that 0.5 mg/day should be the recommended dose in labeling. Further, the similarity in effectiveness of these two doses suggests that a lower dose might be as effective, and be associated with less risk. For this reason, we recommend that the sponsor should evaluate lower doses in a post-marketing study.

Regarding the safety of GILENYA, it is clear that it is associated with numerous adverse effects, including bradycardia and AV block, macular edema, pulmonary complications, infections, and liver injury in patients. In animals, in addition, fingolimod causes fetal injury and malignant lymphomas.

The clinical findings of concern are clearly dose-related, and the incidence of significant adverse events is quite low, and, we agree, acceptable, at the 0.5 mg/day dose. However, we also believe that appropriate monitoring should be undertaken to either detect the onset, or mitigate the risks, of these potential events. Toward this end, we recommend that all patients be monitored for at least 6 hours after the first dose (although a case could be made to monitor only those patients with cardiovascular risk factors, this could be difficult to operationalize, and our only experience in MS patients has been collected under these conditions; we have no information about how well patients will tolerate the first-dose bradycardia in an unsupervised out-patient setting). In addition, we believe that patients should have an ophthalmologic evaluation at baseline and at 3-4 months, as well as at any time they complain of visual symptoms.

Regarding potential pulmonary adverse events, we believe, given the real, but minimal changes seen in PFTs, that routine monitoring is not necessary (especially given the large intra-patient variability in these tests), although appropriate testing should be performed in patients who become symptomatic.

Of considerable concern is the fact that MS patients with significant concomitant illnesses, especially patients with diabetes and cardiovascular disease, were excluded from clinical trials. The experience with the renal transplant program suggests that these patients are at increased risk for many of the adverse events seen with fingolimod, although, of course, the renal patients were treated with much higher doses than 0.5 mg/day. Nonetheless, the lack of data in these

patients at the lower dose is unfortunate, and labeling must make clear that the risks in these patients are unknown. As discussed above, the sponsor has proposed a 5000 patient study in which MS patients with these concomitant illnesses will be enrolled, treated, and followed, and we agree that it will be important for the sponsor to conduct a trial that will by design will be capable of adequately characterize these toxicities of GILENYA in an appropriate MS population.

In addition, an unknown, but important, issue is the potential for GILENYA to cause life-threatening infections and/or cancer at the recommended dose.

The data suggest that serious, life threatening infections can occur in patients treated with GILENYA, though this has not definitively occurred at the 0.5 mg dose. Nonetheless, as exposure at this dose increases, this is a real possibility. In addition, based on GILENYA'S mechanism of action, and the suspicion raised by the results of the mouse carcinogenicity study, the possibility for fingolimod to cause cancer is also real. We believe the proposed large prospective study will yield useful information on these important points.

Given these considerations, we believe that the data taken as a whole support the approval of the NDA. However, the following post marketing studies will be done:

Post-marketing requirements (PMRs)

1) A deferred 24 month randomized study in pediatric patients
2) An observational prospective study comparing fingolimod to another disease modifying treatment. Patients should be representative of the population with MS, and should be evaluated for events of concern (e.g., eye, cardiovascular, pulmonary, hepatic toxicity and infections and lymphoma, sample size to be determined.
3) A pregnancy registry
4) An in vitro study to evaluate the potential for fingolimod-P to induce CYP450 isozymes
5) An in vitro study to evaluate the potential of fingolimod to inhibit CYP2C8 and of fingolimod-P to inhibit CYP2B6
6) An in vitro study to evaluate the potential for statins to induce CYP4F2
7) An integrated summary of safety to include pooled results of previous studies and Study 2309 (the latter study is on-going at this time)
8) A juvenile rat study
9) An interaction study to determine the effects of carbamazepine on fingolimod kinetics

Post-marketing commitments (PMCs)

1) a randomized controlled trial in patients with MS evaluating the safety and effectiveness of fingolimod 0.5 mg/day, 0.25 mg/day, and an appropriate control

In addition, as noted above, the sponsor has proposed a REMS consisting of a Medication Guide and Communication plan; we agree that this is appropriate.

We have agreed with the sponsor on product labeling, the Medication Guide and other elements of the REMS, and on the specific PMRs and PMC. For this reason, we recommend that the NDA be approved.

Russell Katz, M.D.

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/s/

RUSSELL G KATZ
09/21/2010