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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

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