CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	22,527
Applicant Name	Novartis
Date of Submission	December 18, 2009
PDUFA Goal Date	September 21, 2010
Proprietary Name / **Established (USAN) Name**	Gilenya/fingolimod
Dosage Forms / Strength	Oral capsule 0.5 mg
Proposed Indication(s)	1. Treatment of patients with
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Heather Fitter, Lourdes Villalba
Statistical Review	Sharon Yan
Pharmacology Toxicology Review	Richard Siarey (Sup, Lois Freed)
CMC Review/OBP Review	Wendy Wilson (Sup, Martha Heimaan)
Microbiology Review	
Clinical Pharmacology Review	Ju-Ping La, Joo-Yeon Lee
DDMAC	
DSI	
CDTL Review	Eric Bastings, Russell Katz, Sally Yasuda
OSE/DEpi	
OSE/DMEPA	
OSE/DRISK	
Other – Div Dir Review Dep Dir for Safety Review	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

I. Introduction

Dr. Bastings (Deputy Director, Division of Neurology Products) has in his CDTL memo, identified the review team and the very extensive consultation efforts (ophthalmic, cardiology, pulmonary, infectious disease, pediatrics, maternal health, abuse potential) that have contributed to the review of fingolimod treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Dr. Bastings' review also summarizes the effectiveness and safety reviews. As he notes, all CMC issues have been resolved and Dr. Freed has concluded that there are no non-clinical (pharmacology/toxicology) issues that should delay approval. Clinical Pharmacology of fingolimod is complex in a variety of ways, including phosphonglation to an active metabolite (fingolimod P) that remains in dynamic equilibrium with fingolimod, relatively slow (Cmax fingolimod P about 8 hours) but substantially complete (> 85% of dose recovered in urine) absorption, and a variety of modest drug-drug interactions and effects of renal and hepatic impairment. Severe hepatic impairment and concomitant use with ketoconazole increase blood levels (AUC) by about 100%, which could suggest use of a lower dose, but Dr. Bastings suggests an alternative, closer monitoring of such patients, because we have very substantial, and not very adverse, experience with a dose of 1.25 mg/day, more than twice the recommended dose of 0.5 mg. I agree with this alternative. There are no apparent important PK differences related to food, age, gender, or weight, or to the presence of MS. A thorough QT study suggested a modest QT effect, but in trials there was no increase in QTc outliers.

There is reasonable dose-response information for the dose range 0.5-1.25 mg, with no increase in effectiveness at the higher dose but increased toxicity, leading to approval of a single dose and dose strength (0.5 mg). There are no clinical data at lower doses, but modeling of lymphocyte effects (reduction of peripheral lymphocyte counts is the apparent mechanism of action) suggests that a lower dose (0.25 mg) could be effective. There is a post-marketing commitment to study such a dose, and the 0.5 mg dose, with an appropriate control. It seems likely that the study will use interferon as an active control, as a further placebo-controlled trials are unlikely to be acceptable. This should be satisfactory, as in study 2302, the 0.5 mg dose was superior to interferon.

II. Effectiveness

Drs. Bastings and Fitter describe the clinical data, in detail, and there is a detailed statistical review by Sharon Yan.

Study 2301
This was a 2 year randomized, double-blind study comparing 2 doses of fingolimod (0.5 and 1.25 mg) with placebo in patients with relapsing/remitting MS off interferon or COP-1 for ≥ 3 months and off natalizumab for at least 6 months. Neurological exams were performed every 3 months and at the time of suspected relapse and the primary endpoint was relapse rate. A critical secondary endpoint was based on confirmed (over a 3 moth period) disability progression and the time to onset of such confirmed disability progression. MRI evaluations were performed at months 6, 12, and 24 and an additional secondary endpoint was median number of new or enlarging T2 lesions per 24 months.

As shown in the following table, both doses of fingolimod were markedly superior to placebo but similar to each other in affecting randomized relapse rate and in reducing the likelihood of experiencing any relapse episode over the course of the study.

ARR	1.25 mg n =429	0.5 mg n= 425	plbo n = 418
Unadjusted (observed) Adjusted 95% CI p-value % reduction	0.19 0.16 (0.13, 0.19) < 0.001 60%	0.21 0.18 (0.15, 0.22) < 0.001 54%	0.47 0.40 (0.34, 0.47) ------ ------
% free of relapse over study	76%	71%	48%

The difference in ARR between the two doses, although it favored the 1.25 mg dose, was not significant (p = 0.238).

The most critical secondary endpoint was 3 month confirmed disability progression, and both fingolimod doses reduced this rate to a statistically significant extent. As most patients did not have progression (about 25% progression on placebo at 2 years), no change in median time to progression could be estimated, but the percentage of patients without confirmed progression was 83-84% on fingolimod vs 77.5% on placebo, i.e., a roughly 25% reduction in such progression.

The MRI results are shown in the following table:

T2 lesions	1.25 mg n = 337	0.5 mg n = 370	plbo n =339
Number of lesions Median (mean) P-value	 0.0 (2.5) < 0.001	 0.0 (2.5) < 0.001	 5.0 (9.8) -----
% lesion free p-value	51.9 < 0.001	50.5 < 0.001	21.2 -----

Study 2302
Study 2302, with design similar to 2301 compared the 2 doses of fingolimod to interferon beta-la (intramuscular) in a 12 month study, looking at annualized relapse rate, disability progression, and rate of new or newly enlarged T2 lesions on MRI.

ARR	1.25 mg n = 420	0.5 mg n = 429	interferon n = 431
Unadjusted (observed) Adjusted 95% CI p-value % reduction % free of relapse over study	0.26 0.20 (0.16, 0.26) < 0.001 38% 80%	0.21 0.16 (0.12, 0.21) < 0.0001 52% 82%	0.43 0.33 (0.26, 0.41) ---- ---- 70%

It is noteworthy that in this study, unlike 2301, the 0.5 mg dose was slightly favored.

The proportion of patients with 3 month confirmed progression in this 12-month study (i.e. progression present by month 9) was about 6% in the two fingolimod groups vs about 7.5% on interferon, not a

significant difference, but note that in study 2301, progression by month 9 had been seen in about 10% on fingolimod and 14% on placebo.

MRI results, as reanalyzed by Dr. Yan.

T2 Lesions	1.25	0.5	Interferon
Number of lesions Mean p-value	 1.65 0.0017	 1.62 < 0.0007	 2.62 -----

In sum, fingolimod at 0.5 and 1.25 mg reduced AAR by well over 50% compared to placebo and by about 50% compared to interferon. Compared to placebo 3 month disability progression was also substantially reduced compared to placebo but there was not a significant advantage over interferon. Fingolimod was superior to placebo and interferon in reducing the number of new MRI lesions.

III. Safety

Fingolimod's experience raised a number of significant concerns, many of them dose-related and therefore mitigated by use of the lower dose of 0.5 mg, an easy decision as, overall, there was no consistent advantage of the higher dose (slightly better in study 2301, slightly worse in 2302). These safety concerns have been discussed in detail in Dr. Villalba's review, Dr. Yasuda's analysis, and by the various consultants, and are summarized by Dr. Bastings.

Total exposure, as of the 4 month safety update, was over 2600 patients given at least 0.5 mg. At the time of submission (n = 2300), about half had received 1.25 mg, most had been treated in randomized trials, and almost 2000 had been treated for at least 6 months, most of those for 12 months.

There were 9 deaths on fingolimod, 2 from herpes viral infections (one encephalitis, one zoster disseminated both on fingolimod 1.25 mg) considered probably drug related, but with confounding by concomitant use of intravenous steroids, and 2 with rapidly progressing MS. Overall, neoplasms were not increased compared to placebo.

Serious AE's were overall not increased by fingolimod, but there were clearly more cases of bradycardia, AV block, liver enzyme elevations, macular edema, and lymphopenia on fingolimod. Bradycardia, liver enzyme abnormalities, macular edema and infections were most likely to lead to discontinuation of treatment but the rates of these discontinuations were low.

Common AEs notably more frequent on 0.5 mg than placebo include headache, influenza, diarrhea, back pain, liver transaminase elevations and cough.

Specific findings:

1. Leukopenia
Fingolimod cause lymphopenia, falling to about 70% of baseline on 0.5 mg, recovering in about 3 months after discontinuation.

2. Bradycardia/AV Block
First dose of fingolimod (but also first dose of placebo) led commonly to systolic blood pressure < 90 mmHg or a fall of 20 mmHg (23% with 1.25 mg) 19% on 0.5 mg and 16% on placebo with similar falls

of DBP to ≤ 50 mmHg. More important, there was also a marked bradycardic effect (HR < 50 or ≥ 15% fall from baseline) after the first dose. BP effects persisted in about 1.7% of patients on 0.5 mg. Some patients experienced BP elevation, but these were similar in frequency on fingolimod 0.5 mg and placebo.

Troublesome bradycardia occurred within 6 hours of first dosing and resolved within 24 hours, sometimes needing treatment with atropine or isoproterenol. Later doses caused similar effects but these effects decreased during the first month. They can recur, however, after resumption of treatment after discontinuation. AV block was rarely reported as an adverse reaction with the 0.5 mg dose, although Holter monitoring found a considerably higher rate of second degree block (3.4% vs 2% on placebo). The remedy proposed is 6 hours post-dose monitoring in patients after the first dose. A baseline ECG is recommended for patients using beta blockers or CCB's, those with cardiac risk factors such as pre-existing AV block, sick sinus syndrome, heart failure, arrhythmias requiring treatment with Class Ia or III anti-arrhythmias, CAD.

3. Infections
There were relatively few serious infections and the consultant, Dr. Cavaille Coll (Special Pathogens) did not think there was a compelling signal of increased risk. Labeling recommends that a baseline CBC be available before treatment initiation and consideration of suspension of Rx in the event of a serious infection (although the drug persists for about 2 months).

4. Macular edema
Fingolimod causes macular edema but at a low rate with the 0.5 mg dose. There should be an ophthalmologic evaluation at baseline and at 3-4 months after initiation.

5. Respiration
Dose-related persistent (but not progressive and reversible) reduction in FEVI has been seen, together with reduced carbon monoxide diffusion capacity, less clearly non-progressive and reversible, but minimal on the 0.5 mg dose.

6. Hepatic enzyme elevation
Dose-related increases in non-serious AT elevations (ALT > 3x ULN) were seen in 8% of patients on 0.5 mg vs 2% on placebo. There were no instances of serious injury or cases of "Hy's Law" events. Dr. Villalba found one case with elevated bilirubin in a patient with heavy use of alcohol and another case who proved to have hepatitis E. So far no serious liver injury from fingolimod has not been seen but this will bear watching. Baseline liver enzymes should be available before fingolimod is started but there will be no routine monitoring recommendation at this time.

IV. Advisory Committee Meeting

The PCNS AC on June 10, 2010 voted overwhelmingly that fingolimod had been shown to decrease clinical exacerbations and delay accumulation of disability and that the 0.5 mg dose was safe enough to support approval. Most also thought doses < 0.5 mg should be studied after approval. Most of the AC thought the first dose should be given to all patients in a monitored setting, although the cardiologists thought only patients excluded from trials (HR < 60, patients on beta blockers and/or CCBs) needed this. Labeling for the present will recommend monitoring of all patients for bradyarrhythmias. The AC did not urge routine ophthalmologic monitoring. The committee endorsed the sponsors planned 5000 patient post-marketing safety study, expressing particular interest in observing trial-excluded patients (diabetics and people with CV disease). The AC thought fingolimod should be an option for 1st-line treatment, not reserved for failures on other treatment.

V. Conclusions

Fingolimod is an important addition to the MS armamatarium, with effects of both relapse rate and progression, and encouraging effects on MRI. There are a number of post-marketing commitments and requirements, including.

1. Commitment to study a 0.25 mg daily dose.

2. Pediatric study vs active control (interferon).

3. The planned observational study with particular attention to eye toxicity, cardiac and vascular toxicity, pulmonary toxicity, seizures, infections, malignancies, liver toxicity, and atypical MS relapses. The study should compare 2 cohorts, one on fingolimod, the other on other disease-modifying therapy. Patients should include diabetics and people with CV risk factors.

4. Others noted by Dr. Bastings.

5. Approved labeling includes a Medguide reflecting the safety concerns and recommendations described above.

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/s/

ROBERT TEMPLE
09/21/2010