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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA/BLA # **Supplement #**	204063
Applicant Name	Biogen Idec, Inc
Date of Submission	February 24, 2012
PDUFA Goal Date	March 27, 2013
Proprietary Name / **Established (USAN) Name**	Tecfidera (dimethyl fumarate)
Dosage Forms / Strength	delayed-release capsules/120 mg and 240 mg
Proposed Indication(s)	treatment of relapsing forms of multiple sclerosis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Heather Fitter – efficacy; Gerard Boehm - safety
Statistical Review	Xiang Ling
Pharmacology Toxicology Review	Melissa Banks-Muckenfuss; Lois Freed
CMC Review/OBP Review	Sarah Miksinski; David Claffey
Microbiology Review	
Clinical Pharmacology Review	Jagan Parepally
OPDP	Quynh-Van Tran; Meeta Patel
OSI	Michael Skelly
CDTL Review	Billy Dunn
OSE/DEpi	
OSE/DMEPA	Julie Neshiewat
OSE/DRISK	Kendra Worthy
Other – Div Dir Review Dep Dir for Safety Review	

OND=Office of New Drugs
OPDP=Office of Prescription Drug Products
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

This memorandum explains the basis for approval of dimethyl fumarate (Tecfidera), an orally administered drug, for the treatment of patients with relapsing multiple sclerosis. What was studied was relapsing–remitting MS (RRMS) but we have concluded that effectiveness in RRMS supported the broader claim in relapsing MS. My conclusion is based on consideration of individual reviews of clinical, pharmacologic/toxicologic and chemistry data, supervisory reviews, including Dr. Katz's Division Director Review and Dr. Dunn's CDTL review, and Dr. Freed's Pharm/Tox review. The reviewers are listed by subject area and organization (if outside DNP) in Dr. Dunn's CDTL review and Dr. Katz's Division Director review.

Dimethyl fumarate (DMF) is a participant in the tricarboxylic acid (TCA) cycle and is rapidly metabolized to monomethyl fumarate (MMF) and excreted primarily as CO2. Its mechanism of action is not well-established and MMF has a very short half-life (about 1 hour); it is not present in circulation at 24 hours in most patients. Its metabolism and excretion are not likely to be affected by hepatic or renal function or by metabolic enzymes. Food slowed absorption, roughly doubling T_{max} from 2-2.5 hours (fasted state).

The effectiveness of dimethyl fumarate in reducing relapse rates was clearly shown in two well-controlled studies (301, 302) of two years duration; these are extensively described by Drs. Katz and Dunn and I will note only highlights. Both studies showed highly significant and reasonably large reductions in annualized relapse rate (ARR) and in the proportion of patients relapsing (both endpoints were used as primary endpoints, proportion relapsing in study 301 and ARR in study 301), as well as effects on MRI endpoints. Effects on disability progression were also evaluated in both studies, with a significant reduction show in 301 and a favorable trend (but no significant effect) in 302. There appear to be no major differences in demographic subgroups (Fitter).

Clinical studies showed tolerability problems (mainly flushing in about 40% of patients, rarely troubling enough to lead to hospitalization, and GI effects (abdominal pain, diarrhea, nausea, and vomiting), with more of these effects early in treatment than later. Some very modest elevations of aminotransferase were seen (4% vs 2% on placebo) but there was no excess of 3xULN elevations and no associated bilirubin elevations ("Hy's Law" cases). Concerns raised by animal studies with respect to nephrotoxicity and carcinogenicity are discussed extensively by Drs. Dunn, Katz, and Freed and I concur in their conclusions, most importantly because the renal effects of DMF were intensely studied in the DMF database and no adverse effects were observed.

II. Effectiveness

Following a preliminary dose-finding 6-month study (C1900) in RRMS looking at placebo and doses of DMF of 120 mg od, 120 mg tid and 240 mg tid, focusing on decrease of gadolinium-enhancing lesions, which showed a significant effect only at the highest dose, two large trials in RRMS, 301 and 302, were carried out comparing placebo, DMF 240 mg bid and 240 mg tid. Great care was taken in being sure that the reported development of new neurologic symptoms in fact represented a relapse. Symptoms were reported to the treating neurologist or nurse within 48 hours and a phone questionnaire completed. If the treating neurologist thought it was reasonable, an unscheduled relapse assessment was scheduled within 72 hours of symptoms onset and the examining neurologist had to see the patient within 5 days of onset; the examining neurologist performed a relapse assessment and did an expanded disability severity score (EDSS). If the treating neurologist based on the examining neurologist's assessment, concluded that there were new objective findings, the case was referred to the Independent Neurologist Evaluation Committee (INEC), a body of 3 neurologists. If a majority of the INEC, after case review, concluded there was a relapse, it was counted. Only INEC-accepted cases were counted as relapses. This approach is very

sensible (uncharacterized cases will dilute a drug effect) but such an intrepid search for true cases is unusual.

Study 301 results

	Placebo	240 bid	240 tid
Number treated	408	410	416
Proportion relapsing at 2rs (primary) Percent reduction	0.46 ____	0.27 49% p < 0.0001	0.26 49% p < 0.0001
ARR Percent reduction	0.364 ____	0.172 52.7% p < 0.0001	0.189 47.9% p , 0.0001
Proportion with progressing Recent disability reduction	0.27 ____	0.16 38% p = 0.005	0.18 34% p = 0.013

There were also marked reductions (from 17% to 2-4%) in newly enlarging T2 MRI lesions at 2 years.

The study was globally enrolled, with about 1/6 from US.

Study 302 Results

	Placebo	240 bid	240 tid
Number treated	363	359	345
ARR (primary)	0.401 ____	0.224 44.0% p < 0.0001	0.198 50.5% p < 0.0001
Proportion progressive disability	0.17	0.13	0.13
Percent reduction	____	21% p = 0.25	24% p = 0.20

Study 302 did not show significant reduction in disability, although there was a favorable trend.

MRI findings were favorable, as in Study 301.

Overall, the two large controlled studies provide strong evidence of a substantial reduction of relapses in these RRMS patients and some evidence of an effect on progression. Neither study showed a greater effect of tid dosing, so the bid dose will be recommended. Study 302 did include an unblinded (because given by injection) comparator arm, but we do not consider these results adequate to form a conclusion. There are also no data as yet that provide information on whether use of DMF provides additive effects when used with other MS treatments, certainly a matter of future interest.

III. Safety

Dr. Boehm's review, and the reviews by Drs. Katz and Dunn consider safety issues. As noted by Dr. Dunn, Dr. Banks-Muckenfuss (non-clinical) was very concerned about the nephrotoxicity seen in animals, leading her to urge non-approval at this time. Dr. Freed acknowledged the nephrotoxicity, but

noted the lack of similar findings to date in humans, including the substantial experience with Fumaderm (MMF plus DMF) in Germany since 1994, the valuable effect in MS, and the planned further post-marketing study. She , therefore did not believe the animal data were a basis for not approving the drug. I concur with that conclusion, as do Drs. Dunn and Katz.

I agree with Dr. Katz's conclusion that the 9 deaths in the DMF program (7 MS, 2 psoriasis) are not plausibly related to the test drug and that the single cases of SAEs of concern (anaphylaxis, hepatic failure, SJS, rhabdomyolysis, and myopericarditis) had satisfactory alternative explanations.

Flushing (3%) and GI symptoms (about 3%) were the most prominent causes of discontinuation and there were about 9 early cases of flushing, itching, facial edema, some of which were treated with steroids and/or antihistamines. The adverse events in controlled trials were primarily flushing and related AE's (hot flash, erythema, etc), as shown in labeling.

	Placebo 90	240 bid 90
flushing	6	4
abdominal pain	10	18
diarrhea	11	14
nausea	9	12
vomiting	5	9
pruritus	4	8
rash	3	8
erythema	1	5

DMF clearly causes lymphopenia, as discussed by Dr. Katz, but so far this has had no infectious consequences. As noted, minor elevations of aminotransferase (to above ULN) were seen but no difference in frequency of 3x ULN. Dr. Katz discusses 3 cases of more severe injury, including one death from an acetaminophen overdose and two patients with underlying liver disease who did not clearly worsen on treatment. Renal toxicity was prominent in several animal species, but no toxicity was seen in controlled trials; indeed, serum creatinine was slightly reduced on DMF in controlled trials.

In animal carcinogenicity studies (mice and rats), renal tubular adenomas and carcinomas were seen. The controlled clinical data showed no excess of malignancies but would have little power to have done so. As noted, trials also did not show renal toxicity.

Fumaderm, DMF plus MMF, which has been marketed in Germany since 1994 for psoriasis, has had 3 reports of progressive multifocal encephalopathy (PML), a well-recognized consequence of natalizumab, a treatment for MS. This will clearly bear watching.

Post-marketing requirements include a long-term observational study of adult MS patients (at least 5000 followed for a minimum of 5 years. It will look for serious infections, malignancies including renal cell cancer, other serious AE's (hepatic, renal).

IV. Conclusion

Data clearly support a claim for DMF in RRMS and, as Dr. Katz explains, we have broadened such findings to include all relapsing forms of MS, and that is the labeled claim here. The Indications do not specifically refer to the benefits attained, but section 14 of labeling includes both results on relapse rates and progression, although the latter effect is fully supported in only Study 301 (and pooled data for 301

and 302). DMF also appears safe for its intended use. Concerns about nephrotoxicity raised by animal studies did not lead to human renal disease as far as could be determined (serum creatinine actually fell) from an extensive (n – 2210 for MS treatment > 6-months with 1787 > 12 months and 712 > 3 years. As noted, a post-marketing study will follow at least 5000 patients for 5 years.

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/s/

ROBERT TEMPLE
03/27/2013