CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204063Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

DATE: March 17, 2013

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 204063

SUBJECT: Recommendation for action on NDA 204063, for the use of Tecfidera (Dimethyl Fumarate) for the treatment of patients with Relapsing Remitting Multiple Sclerosis (RRMS)

NDA 204063, for the use of Tecfidera (Dimethyl Fumarate) as an oral treatment for patients with Relapsing Remitting Multiple Sclerosis (RRMS), was submitted by Biogen Idec Inc., on 2/27/12. A major amendment, addressing Agency questions related to the carcinogenic potential of the drug, was submitted on 10/5/12; as a result, the user fee goal date is 3/27/13.

The application contains the results of two randomized controlled trials purporting to provide substantial evidence of the drug's effect in the treatment of patients with RRMS. In addition, the application contains safety, non-clinical, clinical pharmacology, and chemistry and manufacturing control (CMC), data that the sponsor believes support the application's approval.

The application has been reviewed by Drs. David Claffey and Sarah Miksinski, Office of New Drug Quality Assessment (ONDQA); Michael Trehy and Anjanette Smith, Division of Pharmaceutical Analysis; Dr. Elsbeth Chikhale, ONDQA, Biopharmaceutics; Drs. Melissa Banks-Muckenfuss and Lois Freed, pharmacology/toxicology; Steve Thomson, Office of Translational Sciences, Office of Biostatistics; Dr. Jagan Parepally, Office of Clinical Pharmacology; Dr. Michael Skelly, Office of Scientific Investigations, Division of Bioequivalence and GLP Compliance; CDER QT Interdisciplinary Review Team; Dr. Heather Fitter, medical reviewer; Dr. Xiang Ling, Office of Biostatistics; Drs. Gerard Boehm and Sally Yasuda, safety team; Dr. Antoine El-Hage, Office of Scientific Investigations, Division of Good Clinical Practice Compliance; Drs. Carrie Ceresa and Nadia Hejazi, Pediatric and Maternal Health Staff; Dr. Alicja Lerner, Controlled Substance Staff; Dr. Andrew Fine, Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance I; Drs. Kendra Worthy and Julie Neshiewat, OSE, Office of Medication Error Prevention and Risk Management; Shawna Hutchins, Office of Medical Policy Initiatives, Division of Medical Policy Programs; Dr. Quynh-Van Tran, Office of Prescription Drug Promotion (OPDP), Division of Professional Drug Promotion; Dr. Meeta Patel, OPDP, Division of Consumer Drug Promotion; Elizabeth Donohoe, Study Endpoints and Labeling Development (SEALD); and Dr. Billy Dunn, neurology team leader and Cross Discipline Team Leader (CDTL).

The review team recommends that the application be approved, albeit with recommendations for the imposition of Post-Marketing Requirements (PMRs).

In this memo, I will briefly review the relevant data, and offer the rationale for the division's recommendations for action on the application.

Background

Dimethyl fumarate (DMF) is rapidly and essentially fully metabolized to the active metabolite monomethyl fumarate (MMF); subsequent metabolism is through the tricarboxylic acid (TCA) cycle, and the active moiety is primarily eliminated as CO_2. Although the precise mechanism of action is unknown, it is believed to activate the nuclear factor related factor 2 (Nrf2) antioxidant response pathway, a pathway believed to upregulate antioxidant response genes.

DMF is not marketed anywhere, but a closely related product, Fumaderm, a combination of DMF and other salts of monoethyl fumarate, has been marketed in Germany since 1994 for the treatment of moderate to severe psoriasis.

Effectiveness

As noted above, the sponsor has submitted the results of two randomized controlled trials of relatively similar design to support a finding of substantial evidence of effectiveness (Studies 301 and 302). In addition, they have submitted the results of another controlled trial (Study C-1900) that served as the basis for the choice of doses studied in Studies 301 and 302. I will briefly review the results of these studies.

C-1900

This was a double-blind, multiple fixed dose study in which patients with RRMS were randomized to receive either placebo, or DMF 120 mg qd, 120 mg tid, or 240 mg tid for 6 months. The primary outcome was the total number of new gadolinium-enhancing lesions measured at Weeks 12, 16, 20, and 24. New or newly enlarging T2 hyperintense lesions at Week 24 were also assessed, as were other MRI measures and annualized relapse rate. From 63-65 patients were randomized to each group.

The following chart displays the relevant results:

	Pbo	120 qd	120 tid	240 tid
Mean new Gd lesions				
Weeks 4-24	6.6	6.2	6.7	3.7
P-value		0.9	0.8	0.002
New enlarging T2				
Hyperintense lesions	4.2	3.8	4.1	2.2
P-value		0.9	0.8	0.0006
New enlarging T1				
Hyperintense lesions	1.7	1.3	1.5	0.8
P-value		0.7	0.8	0.01
Annualized relapse rate	0.65	0.42	0.78	0.44
P-value		0.2	0.6	0.3

Study 301

This was a double blind, multiple fixed dose, multi-center trial in which patients with RRMS were randomized to either placebo, DMF 240 mg BID, or DMF 240 mg TID. The trial duration was two years, and the primary outcome was the proportion of patients relapsing. The study personnel consisted of Primary and Backup Treating Neurologists, Primary and Backup Treating Nurses, and Primary and Backup Examining Neurologists. All study personnel were blinded to treatment assignment. According to Dr. Fitter's very clear explanation, the procedure for documenting that a relapse had occurred is described below:

Patients who experienced new neurologic symptoms were to contact the treating neurologist or nurse within 48 hours. They completed a phone questionnaire, and a determination was made whether an unscheduled relapse assessment visit was necessary. If so, the patient had to have been seen by the treating neurologist within 72 hours of the onset of symptoms, and by the examining neurologist within 5 days of the onset of symptoms. The examining neurologist performed a relapse assessment and an expanded disability severity score (EDSS). Based on the examining neurologist's examination, the treating neurologist determined if there were new objective findings.

If the treating neurologist determined (based on the examining neurologist's exam) that there were new objective findings, the treating neurologist referred the case to the Independent Neurologic Evaluation Committee (INEC), a body of three neurologists. The INEC reviewed the patients' records independently (they

did not meet to discuss the cases). If a majority of the INEC determined that a relapse occurred, it was counted as a relapse. Only INEC-declared relapses were considered in the analyses of relapses.

Subjects could be treated with intravenous methylprednisolone (IVMP) for an acute relapse only after they had been examined by the examining neurologist. If a patient had an INEC-confirmed relapse that occurred at or after Week 24, and had completed 48 weeks of study treatment, they had the following options:

1) remain on blinded treatment
2) switch to open-label alternative MS treatment and remain in the study
3) discontinue study treatment, decline alternative treatment, and remain in the study

Patients who experienced disability progression at any time during the study had the same options.

Other outcome measures included:

1) **Disability Progression**-defined as at least a 1 point increase in the EDSS from a baseline EDSS of at least 1.0 that was sustained for 12 weeks, or a 1.5 point increase in EDSS from a baseline EDSS of 0, sustained for 12 weeks.
2) **Annualized Relapse Rate (ARR)**-including only INEC-confirmed relapses that occurred before a patient received alternative MS treatments
3) **MS Functional Composite (MSFC) Scale**-a three part assessment consisting of a timed 25 foot walk, a 9-Hole Peg Test, and a paced auditory serial addition test 3 (PASAT 3, a cognitive test)
4) **Patient Reported Outcomes**, including:
    1) Global impression of well-being: A visual analogue scale (VAS) from 0-100
    2) SF-36 Health Survey-a 36 item questionnaire with 8 quality of life domains
    3) EQ-5D-consisting of 2 domains; the descriptive system (5 health dimensions) and a VAS

5) **MRI assessments**-

    MRI was assessed at only a subset of sites that had the appropriate facilities and expertise. All MRI scans were centrally read, and assessments were made at baseline and Weeks 24, 48, and 96. A partial list of measures included:

    1) New or enlarging T2 weighted lesion count
    2) T2 weighted lesion volume
    3) Gd-enhancing lesion count

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