CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204063Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	2/11/13
From	Billy Dunn, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	204063
Applicant	Biogen Idec
Date of Submission	2/27/12
PDUFA Goal Date	3/27/13
Proprietary Name / Established (USAN) names	Tecfidera/dimethyl fumarate
Dosage forms / Strength	Oral delayed release capsules/120 mg, 240 mg
Proposed Indication(s)	Treatment of patients with relapsing forms of multiple sclerosis (b) (4)
Recommended:	Approval

1. Introduction

The sponsor (Biogen Idec) has submitted a new drug application (NDA) to support the marketing of dimethyl fumarate (Tecfidera), a new oral drug with a proposed indication for the treatment of patients with relapsing forms of multiple sclerosis (MS) (b) (4) .

Dimethyl fumarate (DMF) has not been previously approved and is categorized as a new molecular entity. A related drug product, a combination of DMF with other fumarate esters including the primary metabolite of DMF, monomethyl fumarate (MMF), was approved in Germany in 1994 for the treatment of psoriasis and is marketed as Fumaderm. The proposed mechanism of action of DMF in MS is activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway that is involved in the cellular response to oxidative stress, ostensibly reducing inflammatory responses in both peripheral and central cells and promoting cytoprotection of central nervous system cells against toxic oxidative insults.

The review team for this NDA included the following primary reviewers:

Chemistry – David Claffey, PhD
Chemistry (Methods Validation Inspection) – Michael Trehy
Chemistry (Biopharmaceutics) – Elsbeth Chikhale, PhD
Office of Manufacturing and Product Quality (Inspections) – Derek Smith, PhD
Nonclinical – Melissa Banks-Muckenfuss, PhD
Nonclinical (Carcinogenicity) – Steven Thomson, PhD
Clinical Pharmacology – Jagan Parepally, PhD

Clinical Pharmacology (IRT-TQT) – Qianyu Dang, PhD
Division of Bioequivalence and GLP Compliance (Inspection) – Michael Skelly, PhD
Statistics – Xiang Ling, PhD
Clinical (Efficacy) – Heather Fitter, MD
Clinical (Safety) – Gerard Boehm, MD
Division of Medication Error Prevention and Analysis – Julie Neshiewat, PharmD
Division of Risk Management – Kendra Worthy, PharmD
Division of Medical Policy Programs – Shawna Hutchins, MPH, RN
Pediatric and Maternal Health Staff (Maternal) – Carrie Ceresa, PharmD
Pediatric and Maternal Health Staff (Pediatric) – Nadia Hejazi, MD
Controlled Substance Staff – Alicja Lerner, MD, PhD
Division of Pharmacovigilance – Andrew Fine, PharmD
Division of Professional Drug Promotion – Quynh-Van Tran, PharmD
Division of Consumer Drug Promotion – Meeta Patel, PharmD
Study Endpoints and Labeling Development – Elizabeth Donohoe, MD
Office of Scientific Investigations – Antoine El-Hage, PhD

I discuss below the key conclusions of each reviewer and provide my recommendations regarding this submission.

2. Background

DMF is not an approved drug product anywhere in the world. It has been under investigational development (IND 73061) in the United States for the treatment of multiple sclerosis since 2006. As noted above, Fumaderm is approved in Germany for the treatment of psoriasis.

As primary support for the proposed indication, the sponsor presents the results from two controlled Phase 3 efficacy study (studies 109MS301 and 109MS302). Both studies were of similar design and evaluated the effect of 240 mg bid and 240 mg tid of DMF in patients with MS on a variety of outcomes. In addition, as further support, the sponsor presents the results of a controlled Phase 2 dose-finding study (study C-1900) and interim results of an ongoing open-label, dose and rater-blinded extension study (109MS303).

One meeting with the sponsor focused on this submission took place, a pre-NDA meeting on 1/25/12. There are no significant outstanding issues from this meeting.

3. CMC/Device

Dr. Claffey reviewed this submission and found it acceptable.

Dr. Chikhale reviewed this submission and found it acceptable.

Mr. Trehy reviewed this submission and found it acceptable.

Dr. Smith completed the manufacturing inspection and found it acceptable.

There are no outstanding CMC issues. There are no CMC post-approval recommendations.

4. Nonclinical Pharmacology/Toxicology

Dr. Thomson reviewed this submission and found the statistical considerations of the carcinogenicity studies acceptable.

Dr. Banks-Muckenfuss reviewed this submission and found it unacceptable. She does not recommend approval. She bases her recommendation on nonclinical findings of renal toxicity, including tumors in rodents, at clinically relevant doses in all species assessed.

As described by Dr. Banks-Muckenfuss, animal data have demonstrated that DMF causes multiple toxicities across organ systems, including "kidney, testes, stomach (nonglandular), pancreas, liver, thymus, lymphatic system, and eye (retina)."

It is the renal toxicity that is most concerning. The renal tubular and interstitial toxicity seen in animals was widespread and somewhat insidious. It appears to occur at lesser doses with increasing duration of exposure, and damage may not clearly be seen in studies of lesser duration. Predictors of toxicity in the animals were not seen consistently in different species (urinary protein only in rats) and the utility of such assessments in humans as predictors of toxicity is uncertain. The renal findings in rodents included renal tumors. These tumors may or may not be species specific. In addition to tumors, the renal findings may be irreversible, as seen in the chronic monkey study.

Dr. Banks-Muckenfuss is concerned that the toxicities, particularly the carcinogenicity, may be compatible with the known actions of DMF. (Dr. Boehm discusses this to some degree, as well). She is perhaps most troubled by the notion that the enhanced clinical monitoring in humans may have been inadequate and that the toxicity may not yet be seen in trials of possibly insufficient duration. Taken together, she is left to conclude that the safety database from the clinical trials was potentially inadequate to detect possible "irreversible tissue damage and loss of function" along with renal tumors associated with human doses of DMF that are linked to relevant toxic doses in animals. She does acknowledge that the relevance of the animal findings to human risk is unclear.

Dr. Banks-Muckenfuss's supervisor, Dr. Lois Freed, performed an independent secondary review with specific attention to renal factors. She, too, observed evidence of widespread multi-organ toxicity across multiple species (rodent, dog, monkey), with clear evidence of renal toxicity.

Upon detailed review of the data, she is somewhat more hopeful, though still cautious, that predictive human monitoring (urinary albumin) may be useful in the avoidance of potential renal toxicity. That said, the chronic toxicity study in monkey and dog resulted in the development of irreversible interstitial fibrosis consistent with low level chronic renal toxicity

and, while BUN and creatinine were decreased (consistent with the findings in rat) there were no urinary findings consistent with renal toxicity.

Given the availability of Fumaderm clinical data, Dr. Freed briefly reviewed its toxicology studies and found a similar, though perhaps somewhat less severe, toxicological profile.

A re-evaluation of mouse and rat carcinogenicity data by the sponsor's expert consultant resulted in no substantial change in the findings of the mouse study but, in the rat study, a reconsideration of the renal tumors resulted in a change in renal tumor incidence such that their incidence was only slightly increased, only in females, and was no longer considered drug-related.

Reproductive and developmental toxicity findings remained significant.

Taken together, Dr. Freed feels the sponsor has conducted an adequate battery of nonclinical studies to support marketing of DMF for treatment of patients with relapsing forms of multiple sclerosis.

She finds that rodent forestomach, rodent and dog testes, and pan-species (mouse, rat, dog, monkey) kidney were the primary target organs. She describes that forestomach is of questionable relevance to humans. She feels that testicular findings can and should be described in clinical labeling. Finally, she agrees with Dr. Banks-Muckenfuss that the data demonstrate a potential for human renal toxicity, suggesting the possibility of irreversible injury due to low level chronic injury and repair.

Recognizing that the review team is in agreement that clinical trial monitoring may not have been able to detect renal injury consistent with that seen in animals, Dr. Freed feels that the efficacy findings in clinical trials along with the available safety data from those clinical trials, limited though it may be, combined with the Fumaderm postmarketing experience (namely, no indication of renal toxicity with longer-term exposure) are sufficient to support approval. She agrees with the plans for the large 5 year observational post-approval study discussed below.

Thus, with appropriate labeling, she recommends approval, along with a nonclinical postmarketing requirement to conduct a juvenile animal toxicology study to support pediatric clinical development.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Parepally, Dr. Dang, and Dr. Skelly reviewed this submission and found it acceptable.

Detailed labeling recommendations are found in the clinical pharmacology review.

The clinical pharmacology review notes that MMF is the active metabolite of DMF and that DMF is not detectable in systemic circulation due to rapid and complete hydrolysis. The conclusions below were based on evaluation of plasma concentrations of MMF.

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