# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204063Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Medication Error Prevention and Risk Management**

# Risk Management Review

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| Date: | February 6, 2013 |
| Reviewer(s): | Kendra Worthy, Pharm. D., Team Leader, Division of Risk Management (DRISK) |
| Division Director | Mary Willy, Ph.D., Director (Acting), DRISK |
| Drug Name(s): | Tecfidera (dimethyl fumarate) delayed release capsules, 120mg, 240mg |
| Indication(s): | Treatment of patients with relapsing multiple sclerosis |
| Application Type/Number: | NDA 204063 |
| Applicant: | Biogen Idec. |

# 1 Introduction

This review documents the Division of Risk Management's (DRISK) evaluation of the need for a risk management strategy for dimethyl fumarate.

Biogen Idec submitted NDA 204063 for Tecfidera (dimethyl fumarate) with the proposed indication for relapsing forms of multiple sclerosis. The applicant did not propose a REMS or a risk management plan (RMP).

# 2 Background

Dimethyl fumarate is under consideration for the treatment of patients with relapsing forms of multiple sclerosis. It is dosed 120 mg orally twice daily for 7 days followed by a maintenance dose of 240 mg orally twice daily. The proposed label states (b) (4)

Dimethyl fumarate (as a combination product with monoethyl fumarate salts) is approved as Fumaderm in Germany for the treatment of psoriasis (1994).

# 3 Regulatory history

## *3.1 Product Labeling*

The FDA-edited proposed labeling includes the following adverse reactions in the Warnings and Precautions section of the labeling.

- Lymphopenia and Risk of Infection
- Flushing

The label does not have a boxed warning.

# 4 Materials reviewed

## *4.1 Data Information Sources*

- Midcycle review slides, Gerald Boehm, M.D., M.P.H. (safety), Medical Officers, Division of Neurology Products (DNP), dated January 9, 2013
- Draft clinical review (efficacy) by Heather Fitter, M.D., FACS, Medical Officers, DNP dated November 8, 2012.
- Clinical review (safety) by Gerald Boehm, M.D., M.P.H., Medical Officers, DNP dated January 9, 2013.
- Draft substantially complete label, Tecfidera (dimethyl fumarate), Biogen Idec, dated February 4, 2013.

# 5 Results of review

## *5.1 Overview of Clinical Program*

Efficacy for the drug was established in two randomized, placebo-controlled trials with 2,665 exposed patients. One trial evaluated safety and efficacy of dimethyl fumarate 240 mg twice daily and 240 mg three times daily compared to placebo, and the second with an additional treatment arm of an "active comparator, Copaxone, in an open label rater blinded only fashion"[1]. Primary endpoints included the proportion of patients relapsing at 2 years (first trial) and the annualized relapse rate (ARR) (second trial). Both trials included secondary endpoints related to MRI findings. The medical officer summarized that "both trials reported very robust findings on the primary clinical measures of relapse and were associated with p values of <0.0001 for all comparisons of active study treatment to placebo"[1], and that "all key secondary MRI endpoints for the active treatment vs. placebo comparisons in both trials were highly supportive ($p<0.0001$) of efficacy". [1]

Safety data was compiled from integrated data from 5 controlled trials with an MS arm (3) and psoriasis arm (2); each arm had open-label extension pools. The applicant also submitted postmarketing safety data for Fumaderm. Eleven deaths occurred; 9 in the treatment arm. Of those 9, seven occurred in the MS trials and 2 in the psoriasis trials. The integrated MS trials mortality was 0.3%, 1.6/1000 PY.[2]

## *5.2 Safety Concerns*

Lymphopenia

In the MS placebo controlled trials, treated patients experienced a 30% mean decline from baseline in lymphocyte count, and the mean lymphocyte count remained reduced at 26% below baseline four weeks after discontinuation. The clinical safety reviewer states that the magnitude of the observed lymphocyte count decline with dimethyl fumarate is within the range of declines described for fingolimod and teriflunomide, two recently approved oral MS treatments.

Flushing

Flushing occurred in over 40% of treated patients. Flushing symptoms generally begin soon after initiating dimethyl fumarate and usually improve or resolve over time. Three percent (3%) of patients discontinued dimethyl fumarate for flushing and <1% had flushing symptoms that were serious. The label states that administration of dimethyl fumarate with food may reduce the incidence of flushing.

Renal toxicity

Kidney changes (tubular and interstitial toxicity) were observed in the preclinical trials in multiple species; however there was no evidence of an increased risk to patients in the

[1] Draft clinical review (efficacy) by Heather Fitter, M.D., FACS, Medical Officers, DNP dated November 8, 2012.

[2] Midcycle review slides, Gerard Joehm, M.D., M P.H., Medical Officer, DNP, dated January 9, 2013.

clinical trials. The applicant states that they intend to monitor this potential risk in the post marketing setting with targeted follow-up of cases suggestive of renal toxicity[3].

Malignancy

Dr. Boehm states in his review that the review team "became aware of publications that identified a metabolite of dimethyl fumarate, fumarate, as an 'oncometabolite", so the Agency extended the PDUFA goal date to examine additional data from the sponsor regarding this metabolite. He goes on to state:

> *"The medical literature explains that mutations resulting in significant declines or loss of fumarate hydratase (FH) function result in increased intracellular levels of fumarate. Increased intracellular levels of fumarate are presumed to be responsible for the sequelae of leiomyomata and renal cell cancers seen in the Hereditary Leiomyoma and Renal Cell Cancer (HLRCC) syndrome.*
>
> *We lack information to determine if ingesting [dimethyl fumarate] results in increased intracellular levels of fumarate. Fumarate was not detected in plasma levels of patients administered DMF, but this does not necessarily preclude the possibility of increased intracellular fumarate levels.*
>
> *The available NDA data do not suggest that treatment with [dimethyl fumarate] results in the outcomes seen with reduced FH function. While this difference may be because treatment with [dimethyl fumarate] does not result in the increased intracellular fumarate levels seen with FH deficiency, as Biogen proposes, we do not currently have data to confirm this hypothesis."*[3]

Dr. Boehm also recommended that the applicant monitor post marketing reports to identify cases of leiomyomata and or renal cell cancers in patients treated with dimethyl fumarate.

Elevated Liver Enzymes

Elevated hepatic transaminases were observed in the treatment (4%) and placebo (2%) groups in clinical trials, with the majority of the elevations being < 3 times the upper limit of normal (ULN). The increased incidence of elevations of hepatic transaminases in patients treated with dimethyl fumarate relative to placebo was primarily seen during the first six months of treatment and occurred at levels < 3 times the ULN. Discontinuations due to elevations in hepatic transaminases were < 1% and were similar in both the treatment and placebo groups.[4]

[3] Clinical review (safety) by Gerald Boehm, M.D., M.P.H., Medical Officers, DNP dated January 9, 2013.

[4] Draft substantially complete label, Tecfidera (dimethyl fumarate), Biogen Idec.

## *5.3 Applicant's Proposal for Risk Management*

The applicant did not propose a REMS or RMP for dimethyl fumarate.

# 6 Discussion

MS is a chronic demyelinating disorder of the central nervous system that can lead to progressive neurological disability. Treatment goals for MS are to shorten the duration and severity of symptoms associated with relapses, prevent the incidence of relapses, and delay the accumulation of disability.[5] Dimethyl fumarate, an oral formulation, was found efficacious in reducing the frequency of clinical exacerbations as well as delaying the accumulation of physical disability with "no safety issues that preclude approval".[6] The other approved oral treatments for relapsing MS are Aubagio (Teriflunomide) and Gilenya (fingolimod).

**REMS Considerations**

Products used for the treatment of relapsing MS have a mixed safety profile; two products have safety risks that required REMS to ensure that the benefits outweigh the risks:

- Gilenya (fingolimod) (oral) has a REMS consisting of a communication plan to inform healthcare providers about the serious risks associated with the drug, which includes bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk.

- Tysabri (infusion) has a REMS consisting of elements to assure safe use (ETASU) to promote early diagnosis and timely discontinuation of Tysabri in the event of suspected progressive multifocal leukoencephalopathy (PML). The REMS also informs prescribers, infusion center healthcare providers, and patients about the risks associated with Tysabri, in addition to warning against concurrent use with antineoplastic, neosuppressant, or immunomodulating agents, and in patients who are immunocompromised.

Products approved for the treatment of relapsing forms of MS that do not have an approved REMS include:

- Avonex, Rebif, Betaseron (Recombinant interferon-b) (subcutaneous)

- Copaxone (glatiramer acetate) (subcutaneous)

- Mitoxantrone (infusion)

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[5] Draft clinical review (efficacy) by Heather Fitter, M.D , FACS, Medical Officers, DNP dated November 8, 2012.

[6] Clinical review (safety) by Gerald Boehm, M.D , M.P.H., Medical Officers, DNP dated January 9, 2013.

- Aubagio (Teriflunomide) (oral)

Please see Table 1 appended to this review (completed by Dr. Fitter) for a comparison of these products.

# 7 Conclusion

After review of the safety data, DRISK concludes that a REMS for Tecfidera (dimethyl fumarate) is not necessary at this time. The risks identified at this time can be managed adequately through labeling and routine pharmacovigilance. Should DNP identify additional safety information that warrants risk mitigation measures, please send a consult to DRISK.

**Table 1: Table of currently available treatments for proposed indication**

Draft clinical review (efficacy) by Heather Fitter, M D., FACS, Medical Officers, DNP dated November 8, 2012.

| | Indication | Effect on exacerbation (exac) rate | | Effect on disability progression | Safety issues (of concern) | Approved dose |
|---|---|---|---|---|---|---|
| **Avonex[¥] (RMS)** | Decrease clinical exac, slow physical disability | 32% reduction (rn) | | 37% rn | decreased blood counts, hepatic injury, flu like symptoms | 30 mcg IM q week |
| **Betaseron[¥] (RMS)** | Decrease clinical exac | 30% reduction | | None described in label | injection site necrosis, flu like symptoms | 0.25 mg sq qod |
| **Rebif[¥] (RMS)** | Decrease clinical exac, delay physical disability | 22 mcg<br>29% rn | 44 mcg<br>32 % rn vs. placebo and Avonex* | 27% rn | hepatic injury, flu like symptoms, injection site reaction | 22 mcg or 44 mcg tiw |
| **Copaxone (glatiramer acetate) (RMS)** | Reduce relapses including patients with CIS | 75% rn in first trial (n=48)<br>29% rn in second trial (n=251) | | None described in label | Post injection reaction, transient chest pain, skin necrosis | 20 mg sq q d |
| **Mitoxantrone (SPMS or worsening RRMS)** | Reduce neurologic disability and/or relapses | 60% rn exacerbations;<br>Primary outcome: 86% rn in new enhancing lesions | | 64% rn | Cumulative cardiotoxicity, AML[1] | 12mg/m2 IV q 3 months |
| **Tysabri (natalizumb) (RMS)** | To delay physical disability and reduce exac | 61% rn | | 33% rn | PML[2], immunosuppression, hepatotoxicity | 300 mg IV q 4 weeks |
| **Gilenya (fingolimod) (RMS)** | Decrease ARR and reduce disability progression | 54% rn | | 30% rn | Bradycardia, macular edema, infection | 0.5 mg po q day |
| **Teriflunamide** | Treatment of RMS | 32% rn | | 26% rn for 14 mg | Hepatotoxic, Teratogenic | 7 mg or 14 mg po q d |

[1] acute myelogenous leukemia

[2] progressive multifocal leukoencephalopathy

[¥] Recombinant interferon-b

*32% reduction in proportion of Rebif patients who experienced relapses compared to Avonex.

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/s/

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KENDRA C WORTHY
02/06/2013

MARY E WILLY
02/06/2013
I concur