# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204063Orig1s000

# OTHER REVIEW(S)

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**MEMORANDUM**

**DEPARTMENT OF HEALTH & HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**

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**Division of Neurology Products (HFD-120)**
**Center for Drug Evaluation and Research**

Date: March 20, 2013

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 204-063 (BG-00012, dimethyl fumarate, TECFIDERA), labeling recommendations.

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Recommendations for labeling are provided in this memo; the sponsor's proposed labeling was used as the base document. These labeling recommendations take into account those provided by Dr. Banks-Muckenfuss (*cf. Pharmacology/Toxicology NDA Review and Evaluation, NDA 204063, Melissa K. Banks-Muckenfuss, Ph.D., 1/28/2013*) and some, but not all, of the additional comments provided by the sponsor. Plasma exposure (AUC) margins were calculated using values in humans from repeat-dose studies (# 109HV103 and 109HV104): $C_{max}$: 2.24-2.4 μg/mL; AUC: 10-11.3 μg*hr/mL.

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| SPONSOR | RECOMMENDED |
|---|---|
| **HIGHLIGHTS OF PRESCRIBING INFORMATION** | |
| **-----INDICATIONS AND USAGE-----** | **-----INDICATIONS AND USAGE-----** |
| (b) (4) | TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis. (1) |
| | **----USE IN SPECIFIC POPULATIONS-----** |
| | Pregnancy: based on animal data, may cause fetal harm. (8.1) |
| | |
| | **8 USE IN SPECIFIC POPULATIONS** |
| | **8.1 Pregnancy**<br>Pregnancy Category C<br><br>There are no adequate and well-controlled studies in pregnant women. In animals, adverse effects on offspring survival, growth, sexual maturation, and neurobehavioral function were observed when dimethyl fumarate (DMF) was administered during pregnancy and lactation at clinical relevant doses. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.<br><br>In rats administered DMF orally (25, 100, 250 mg/kg/day) throughout organogenesis, embryofetal toxicity (reduced fetal body weight and delayed ossification) were observed at the highest dose tested. This dose also produced evidence of maternal toxicity (reduced body weight). Plasma exposure (AUC) for monomethyl fumarate (MMF), the major circulating metabolite, at the no-effect dose is approximately three times that in humans at the recommended human dose (RHD) of 480 mg/day. In rabbits administered DMF orally (25, 75, and 150 mg/kg/day) throughout organogenesis, embryolethality and decreased maternal body weight were observed at the highest dose tested. The plasma AUC for MMF at the no-effect dose is approximately 5 times that in humans at the RHD.<br><br>Oral administration of DMF (25, 100, and 250 mg/kg/day) to rats throughout organogenesis and lactation resulted in increased lethality, persistent reductions in body weight, delayed sexual maturation (male and female pups), and reduced testicular weight in offspring at the highest dose tested. Neurobehavioral impairment was observed at all doses. A no-effect dose for developmental |

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| | |
|---|---|
| (b) (4) | toxicity was not identified. The lowest dose tested was associated with plasma AUC for MMF lower than that in humans at the RHD.<br><br>Pregnancy Registry<br><br>*[No comment on PR wording; defer to clinical team.]* |
| | *This section should be omitted.* |
| **8.3 Nursing Mothers**<br><br>It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRADENAME is administered to a nursing woman. | **8.3 Nursing Mothers**<br><br>It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TECFIDERA is administered to a nursing woman. |
| (b) (4) | **8.4 Pediatric Use**<br><br>Safety and effectiveness in pediatric patients not been established. |
| **12 CLINICAL PHARMACOLOGY** | |
| (b) (4) | **12.1 Mechanism of Action**<br><br>The mechanism by which dimethyl fumarate (DMF) exerts its therapeutic effect in multiple sclerosis is unknown. DMF and the metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist *in vitro*. |
| **13 NONCLINICAL TOXICOLOGY** | |

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(b) (4)

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

*Carcinogenesis*
Carcinogenicity studies of dimethyl fumarate (DMF) were conducted in mouse and rat. In mouse, oral administration of DMF (25, 75, 200 and 400 mg/kg/day) for up to two years resulted in an increase in nonglandular stomach (forestomach) and kidney tumors: squamous cell carcinomas and papillomas of the forestomach in males and females at 200 and 400 mg/kg/day; leiomyosarcomas of the forestomach at 400 mg/kg/day in males and females; renal tubular adenomas and carcinoma at 200 and 400 mg/kg/day in males; and renal tubule adenomas at 400 mg/kg/day in females. Plasma MMF exposure (AUC) at the highest dose not associated with tumors in mouse (75 mg/kg/day) was similar to that in humans at the recommended human dose (RHD) of 480 mg/day.

In rat, oral administration of DMF (25, 50, 100, and 150 mg/kg/day) for up to two years resulted in increases in squamous cell carcinomas and papillomas of the forestomach at all doses tested in males and females, and in testicular interstitial (Leydig) cell adenomas at 100 and 150 mg/kg/day. Plasma MMF AUC at the lowest dose tested was lower than that in humans at the RHD.

*Mutagenesis*
Dimethyl fumarate and monomethyl fumarate (MMF) were not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. DMF and MMF were clastogenic in the in vitro chromosomal aberration assay in human peripheral blood lymphocytes in the absence of metabolic activation. DMF was not clastogenic in the in vivo micronucleus assay in rat.

*Impairment of Fertility*
In male rat, oral administration of DMF (75, 250, and 375 mg/kg/day) prior to and throughout the mating period had no effect on fertility; however, increases in non-motile sperm were observed at the mid and high doses. The no-effect dose for adverse effects on sperm is similar to the recommended human dose (RHD) of 480 mg/day on a body surface area ($mg/m^2$) basis.

In female rat, oral administration of DMF (20, 100, and 250 mg/kg/day) prior to and during mating and continuing to gestation day 7 caused disruption of the estrus cycle and increases in embryolethality at the highest dose tested. The highest dose not associated with adverse effects (100 mg/kg/day) is

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