CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 204063/S-10

Trade Name: Tecfidera

Generic Name: Dimethyl fumarate

Sponsor: Biogen IDEC Inc.

Approval Date: December 03, 2014

Indications: For the treatment of patients with relapsing forms of multiple sclerosis.

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APPLICATION NUMBER:

NDA 204063/S-10

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204063/S-10

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063/S-003, S-008, and S-010 **SUPPLEMENT APPROVAL**

Biogen Idec
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Supplemental New Drug Applications (sNDA):

Application	Product Name	Submitted on:	Received on:
NDA 204063/S-003	Tecfidera (dimethyl fumarate)	January 31, 2014	February 3, 2014
This supplement, submitted as a "Prior Approval supplement," proposes:			
The (b) (4) temporary dose reduction to manage flushing and gastrointestinal side effects associated with Tecfidera treatment.			

Application	Product Name	Submitted on:	Received on:
NDA 204063/S-008	Tecfidera (dimethyl fumarate)	July 28, 2014	July 28, 2014
This supplement, submitted as a "Prior Approval supplement," proposes changes to:			
Highlights and Section 4: Contraindication for patients with known hypersensitivity to dimethyl fumarate or to any of the excipients of Tecfidera Section 5.1: Hypersensitivity reactions (section added) Section 8.1: Pregnancy registry phone number updated and website added			

Application	Product Name	Submitted on:	Received on:
NDA 204063/S-010	Tecfidera (dimethyl fumarate)	November 6, 2014	November 6, 2014
This supplement, submitted as a "Prior Approval supplement," proposes changes to:			
Highlights: Warnings and Precautions Section 2.1 – Dosing and Administration Section 5.2 – Progressive Multifocal Leukoencephalopathy (section added) Section 5.3 – Lymphopenia Section 17 – Patient Counseling Information Patient Information			

We also acknowledge receipt of your amendments to NDA 204063/S-003 dated February 21, 2014 and November 19, 2014; NDA 204063/S-008 dated August 25, 2014, October 17, 2014, October 23, 2014, and October 29, 2014; and NDA 204063/S-010 dated November 7, 2014, November 25, 2014, November 26, 2014, and December 3, 2014.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in these supplements, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Laurie Kelley, PA-C, Regulatory Project Manager, via telephone at (301) 796-5068 or via email at Laurie.Kelley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
12/03/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204063/S-10

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TECFIDERA safely and effectively. See full prescribing information for TECFIDERA.

TECFIDERA® (dimethyl fumarate) delayed-release capsules, for oral use
Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Dosage and Administration, Dosing Information (2.1)	12/2014
Contraindications (4)	12/2014
Warnings and Precautions, Anaphylaxis and Angioedema (5.1)	12/2014
Warnings and Precautions, PML (5.2)	12/2014
Warnings and Precautions, Lymphopenia (5.3)	12/2014

INDICATIONS AND USAGE

TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (1)

DOSAGE AND ADMINISTRATION

- Starting dose: 120 mg twice a day, orally, for 7 days (2.1)
- Maintenance dose after 7 days: 240 mg twice a day, orally (2.1)
- Swallow TECFIDERA capsules whole and intact. Do not crush, chew, or sprinkle capsule contents on food (2 1)
- Take TECFIDERA with or without food (2.1)

DOSAGE FORMS AND STRENGTHS

Delayed-release capsules: 120 mg and 240 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and angioedema: Discontinue and do not restart TECFIDERA if these occur. (5.1)
- Progressive multifocal leukoencephalopathy (PML): Withhold TECFIDERA at the first sign or symptom suggestive of PML. (5.2)
- Lymphopenia: Obtain a CBC including lymphocyte count before initiating TECFIDERA, after 6 months, and every 6 to 12 months thereafter. Consider interruption of TECFIDERA if lymphocyte counts <0 5 x 10^9/L persist for more than six months. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10% and ≥2% placebo) were flushing, abdominal pain, diarrhea, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen Idec at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The starting dose for TECFIDERA is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally. TECFIDERA should be swallowed whole and intact. TECFIDERA should not be crushed or chewed and the capsule contents should not be sprinkled on food. TECFIDERA can be taken with or without food.

Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dose of 240 mg twice a day should be resumed. Discontinuation of TECFIDERA should be considered for patients unable to tolerate return to the maintenance dose. The incidence of flushing may be reduced by administration of TECFIDERA with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing *[see Clinical Pharmacology (12.3)]*.

2.2 Blood Test Prior to Initiation of Therapy

Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

TECFIDERA is available as hard gelatin delayed-release capsules containing 120 mg or 240 mg of dimethyl fumarate. The 120 mg capsules have a green cap and white body, printed with “BG-12 120 mg” in black ink on the body. The 240 mg capsules have a green cap and a green body, printed with “BG-12 240 mg” in black ink on the body.

4 CONTRAINDICATIONS

TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or to any of the excipients of TECFIDERA. Reactions have included anaphylaxis and angioedema *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Angioedema

TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms have included difficulty breathing, urticaria, and swelling of the throat and tongue. Patients should be instructed to discontinue TECFIDERA and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema.

5.2 Progressive Multifocal Leukoencephalopathy

A fatal case of progressive multifocal leukoencephalopathy (PML) occurred in a patient with MS who received TECFIDERA for 4 years while enrolled in a clinical trial. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. During the clinical trial, the patient experienced prolonged lymphopenia (lymphocyte counts predominantly $<0.5x10^9$/L for 3.5 years) while taking TECFIDERA *[see Warnings and Precautions (5.3)]*. The role of lymphopenia in this case is unknown. The patient had no other identified systemic medical conditions resulting in compromised immune system function and had not previously been treated with natalizumab, which has a known association with PML. The patient was also not taking any immunosuppressive or immunomodulatory medications concomitantly.

At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

5.3 Lymphopenia

TECFIDERA may decrease lymphocyte counts. In the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with TECFIDERA and then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but did not return to baseline. Six percent (6%) of TECFIDERA patients and <1% of placebo patients experienced lymphocyte counts $<0.5x10^9$/L (lower limit of normal $0.91x10^9$/L). The incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with TECFIDERA or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8x10^9$/L or $0.5x10^9$/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly $<0.5x10^9$/L for 3.5 years) *[see Warnings and Precautions (5.2)]*. In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts $<0.5 \times 10^9$/L for at least six months. In these patients, the majority of lymphocyte counts remained $<0.5x10^9$/L with continued therapy. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

Before initiating treatment with TECFIDERA, a CBC including lymphocyte count should be obtained. A CBC including lymphocyte count should also be obtained after 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated. Consider interruption of

TECFIDERA in patients with lymphocyte counts <0.5 x 10^9/L persisting for more than six months. Given the potential for delay in lymphocyte recovery after discontinuation of TECFIDERA, consider following lymphocyte counts until lymphopenia is resolved. Withholding treatment should be considered in patients with serious infections until the infection(s) is resolved. Decisions about whether or not to restart TECFIDERA should be individualized based on clinical circumstances.

5.4 Flushing

TECFIDERA may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). In clinical trials, 40% of TECFIDERA treated patients experienced flushing. Flushing symptoms generally began soon after initiating TECFIDERA and usually improved or resolved over time. In the majority of patients who experienced flushing, it was mild or moderate in severity. Three percent (3%) of patients discontinued TECFIDERA for flushing and <1% had serious flushing symptoms that were not life-threatening but led to hospitalization. Administration of TECFIDERA with food may reduce the incidence of flushing. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing *[see Dosing and Administration (2.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in labeling:

- Anaphylaxis and Angioedema *[see Warnings and Precautions (5.1)]*.
- Progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.2)]*.
- Lymphopenia *[see Warnings and Precautions (5.3)]*.
- Flushing *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common adverse reactions (incidence ≥10% and ≥2% more than placebo) for TECFIDERA were flushing, abdominal pain, diarrhea, and nausea.

Adverse Reactions in Placebo-Controlled Trials

In the two well-controlled studies demonstrating effectiveness, 1529 patients received TECFIDERA with an overall exposure of 2244 person-years *[see Clinical Studies (14)]*.

The adverse reactions presented in the table below are based on safety information from 769 patients treated with TECFIDERA 240 mg twice a day and 771 placebo-treated patients.

Table 1: Adverse Reactions in Study 1 and 2 reported for TECFIDERA 240 mg BID at ≥ 2% higher incidence than placebo

	TECFIDERA N=769 %	Placebo N=771 %
Flushing	40	6
Abdominal pain	18	10
Diarrhea	14	11
Nausea	12	9
Vomiting	9	5
Pruritus	8	4
Rash	8	3
Albumin urine present	6	4
Erythema	5	1
Dyspepsia	5	3
Aspartate aminotransferase increased	4	2
Lymphopenia	2	<1

Gastrointestinal

TECFIDERA caused GI events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). The incidence of GI events was higher early in the course of treatment (primarily in month 1) and usually decreased over time in patients treated with TECFIDERA compared with placebo. Four percent (4%) of patients treated with TECFIDERA and less than 1% of placebo patients discontinued due to gastrointestinal events. The incidence of serious GI events was 1% in patients treated with TECFIDERA.

Hepatic Transaminases

An increased incidence of elevations of hepatic transaminases in patients treated with TECFIDERA was seen primarily during the first six months of treatment, and most patients with elevations had levels < 3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase to ≥ 3 times the ULN occurred in a small number of patients treated with both TECFIDERA and placebo and were balanced between groups. There were no elevations in transaminases ≥ 3 times the ULN with concomitant elevations in total bilirubin > 2 times the ULN. Discontinuations due to elevated hepatic transaminases were < 1% and were similar in patients treated with TECFIDERA or placebo.

Eosinophilia

A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

Adverse Reactions in Placebo-Controlled and Uncontrolled Studies

In placebo-controlled and uncontrolled clinical studies, a total of 2513 patients have received TECFIDERA and been followed for periods up to 4 years with an overall exposure of 4603 person-years. Approximately 1162 patients have received more than 2 years of treatment with TECFIDERA. The adverse reaction profile of TECFIDERA in the uncontrolled clinical studies was consistent with the experience in the placebo-controlled clinical trials.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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 clinically relevant doses. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

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 at the highest dose tested. Neurobehavioral impairment was observed at all doses. A no-effect dose for developmental toxicity was not identified. The lowest dose tested was associated with plasma AUC for MMF lower than that in humans at the RHD.

Pregnancy Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to TECFIDERA during pregnancy. Encourage patients to enroll by calling 1-866-810-1462 or visiting www.tecfiderapregnancyregistry.com.

8.3 Nursing Mothers

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.

8.4 Pediatric Use

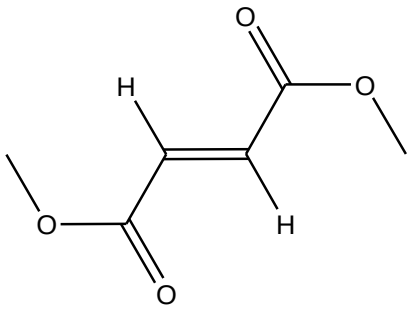
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of TECFIDERA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

TECFIDERA contains dimethyl fumarate which is also known by its chemical name, dimethyl (E) butenedioate, ($C_6H_8O_4$). It has the following structure:



Dimethyl fumarate is a white to off-white powder that is highly soluble in water with a molecular mass of 144.13.

TECFIDERA is provided as hard gelatin delayed-release capsules for oral administration, containing 120 mg or 240 mg of dimethyl fumarate consisting of the following inactive ingredients: microcrystalline cellulose, silicified microcrystalline cellulose, croscarmellose sodium, talc, silica colloidal silicon dioxide, magnesium stearate, triethyl citrate, methacrylic acid copolymer - Type A, methacrylic acid copolymer dispersion, simethicone (30% emulsion), sodium lauryl sulphate, and polysorbate 80. The capsule shell, printed with black ink, contains the following inactive ingredients: gelatin, titanium dioxide, FD&C blue 1; brilliant blue FCF, yellow iron oxide and black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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*.

12.2 Pharmacodynamics

Potential to prolong the QT interval

In a placebo controlled thorough QT study performed in healthy subjects, there was no evidence that dimethyl fumarate caused QT interval prolongation of clinical significance (i.e., the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 ms).

12.3 Pharmacokinetics

After oral administration of TECFIDERA, dimethyl fumarate undergoes rapid presystemic hydrolysis by esterases and is converted to its active metabolite, monomethyl fumarate (MMF). Dimethyl fumarate is not quantifiable in plasma following oral administration of TECFIDERA. Therefore all pharmacokinetic analyses related to TECFIDERA were performed with plasma MMF concentrations. Pharmacokinetic data were obtained in subjects with multiple sclerosis and healthy volunteers.

Absorption

The median T_{max} of MMF is 2-2.5 hours. The peak plasma concentration (C_{max}) and overall exposure (AUC) increased approximately dose proportionally in the dose range studied (120 mg to 360 mg). Following administration of TECFIDERA 240 mg twice a day with food, the mean C_{max} of MMF was 1.87 mg/L and AUC was 8.21 mg.hr/L in MS patients.

A high-fat, high-calorie meal did not affect the AUC of MMF but decreased its Cmax by 40%. The T_{max} was delayed from 2.0 hours to 5.5 hours. In this study, the incidence of flushing was reduced by approximately 25% in the fed state.

Distribution

The apparent volume of distribution of MMF varies between 53 and 73 L in healthy subjects. Human plasma protein binding of MMF is 27-45% and independent of concentration.

Metabolism

In humans, dimethyl fumarate is extensively metabolized by esterases, which are ubiquitous in the gastrointestinal tract, blood, and tissues, before it reaches the systemic circulation. Further metabolism of MMF occurs through the tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP) system. MMF, fumaric and citric acid, and glucose are the major metabolites in plasma.

Elimination

Exhalation of CO_2 is the primary route of elimination, accounting for approximately 60% of the TECFIDERA dose. Renal and fecal elimination are minor routes of elimination, accounting for 16% and 1% of the dose respectively. Trace amounts of unchanged MMF were present in urine.

The terminal half-life of MMF is approximately 1 hour and no circulating MMF is present at 24 hours in the majority of individuals. Accumulation of MMF does not occur with multiple doses of TECFIDERA.

Specific Populations

Body weight, gender, and age do not require dosage adjustment.

No studies have been conducted in subjects with hepatic or renal impairment. However, neither condition would be expected to affect exposure to MMF and therefore no dosage adjustment is necessary.

Drug Interaction Studies

No potential drug interactions with dimethyl fumarate or MMF were identified in *in vitro* CYP inhibition and induction studies, or in P-glycoprotein studies. Single doses of interferon beta-1a or glatiramer acetate did not alter the pharmacokinetics of MMF. Aspirin, when administered approximately 30 minutes before TECFIDERA, did not alter the pharmacokinetics of MMF.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of dimethyl fumarate (DMF) were conducted in mice and rats. In mice, 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 carcinomas 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 mice (75 mg/kg/day) was similar to that in humans at the recommended human dose (RHD) of 480 mg/day.

In rats, 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 (DMF) 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 the rat.

Impairment of Fertility

In male rats, 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 rats, 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 estrous cycle and increases in embryolethality at the highest dose tested. The highest dose not associated with adverse effects (100 mg/kg/day) is twice the RHD on a mg/m^2 basis.

Testicular toxicity (germinal epithelial degeneration, atrophy, hypospermia, and/or hyperplasia) was observed at clinically relevant doses in mice, rats, and dogs in subchronic and chronic oral toxicity studies of DMF, and in a chronic oral toxicity study evaluating a combination of four fumaric acid esters (including DMF) in rats.

13.2 Animal Toxicology and/or Pharmacology

Kidney toxicity was observed after repeated oral administration of dimethyl fumarate (DMF) in mice, rats, dogs, and monkeys. Renal tubule epithelia regeneration, suggestive of tubule epithelial injury, was observed in all species. Renal tubular hyperplasia was observed in rats with dosing for up to two years. Cortical atrophy and interstitial fibrosis were observed in dogs and monkeys at doses above 5 mg/kg/day. In monkeys, the highest dose tested (75 mg/kg/day) was associated with single cell necrosis and multifocal and diffuse interstitial fibrosis, indicating irreversible loss of renal tissue and function. In dogs and monkeys, the 5 mg/kg/day dose was associated with plasma MMF exposures less than or similar to that in humans at the recommended human dose (RHD).

A dose-related increase in incidence and severity of retinal degeneration was observed in mice following oral administration of DMF for up to two years at doses above 75 mg/kg/day, a dose associated with plasma MMF exposure (AUC) similar to that in humans at the RHD.

14 CLINICAL STUDIES

The efficacy and safety of TECFIDERA were demonstrated in two studies (Studies 1 and 2) that evaluated TECFIDERA taken either twice or three times a day in patients with relapsing-remitting multiple sclerosis (RRMS). The starting dose for TECFIDERA was 120 mg twice or three times a day for the first 7 days, followed by an increase to 240 mg twice or three times a day. Both studies included patients who had experienced at least 1 relapse over the year preceding the trial or had a brain Magnetic Resonance Imaging (MRI) scan demonstrating at least one gadolinium-enhancing (Gd+) lesion within 6 weeks of randomization. The Expanded Disability Status Scale (EDSS) was also assessed and patients could have scores ranging from 0 to 5. Neurological evaluations were performed at baseline, every 3 months, and at the time of suspected relapse. MRI evaluations were performed at baseline, month 6, and year 1 and 2 in a subset of patients (44% in Study 1 and 48% in Study 2).

Study 1: Placebo-Controlled Trial in RRMS

Study 1 was a 2-year randomized, double-blind, placebo-controlled study in 1234 patients with RRMS. The primary endpoint was the proportion of patients relapsed at 2 years. Additional endpoints at 2 years included the number of new or newly enlarging T2 hyperintense lesions, number of new T1 hypointense lesions, number of Gd+ lesions, annualized relapse rate (ARR), and time to confirmed disability progression. Confirmed disability progression was defined as at least a 1 point increase from baseline EDSS (1.5 point increase for patients with baseline EDSS of 0) sustained for 12 weeks.

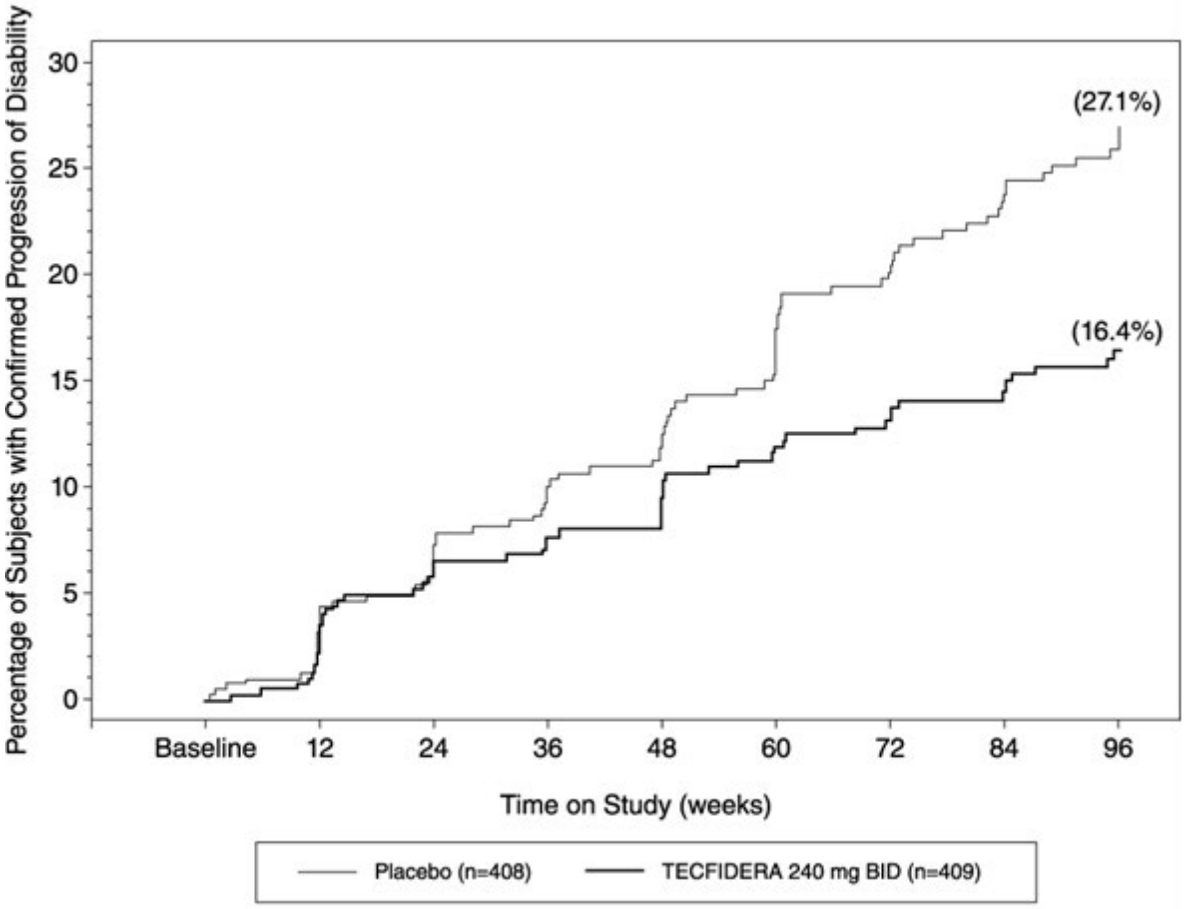
Patients were randomized to receive TECFIDERA 240 mg twice a day (n=410), TECFIDERA 240 mg three times a day (n=416), or placebo (n=408) for up to 2 years. The median age was 39 years, median time since diagnosis was 4 years, and median EDSS score at baseline was 2. The median time on study drug for all treatment arms was 96 weeks. The percentages of patients who completed 96 weeks on study drug per treatment group were 69% for patients assigned to TECFIDERA 240 mg twice a day, 69% for patients assigned to TECFIDERA 240 mg three times a day and 65% for patients assigned to placebo groups.

TECFIDERA had a statistically significant effect on all of the endpoints described above and the 240 mg three times daily dose showed no additional benefit over the TECFIDERA 240 mg twice daily dose. The results for this study (240 mg twice a day vs. placebo) are shown in Table 2 and Figure 1.

Table 2: Clinical and MRI Results of Study 1

	TECFIDERA 240 mg BID	Placebo	P-value
Clinical Endpoints	N=410	N=408	
Proportion relapsing (primary endpoint) Relative risk reduction	27% 49%	46%	<0.0001
Annualized relapse rate Relative reduction	0.172 53%	0.364	<0.0001
Proportion with disability progression Relative risk reduction	16% 38%	27%	0.0050
MRI Endpoints	N=152	N=165	
Mean number of new or newly enlarging T2 lesions over 2 years	2.6	17	<0.0001
Percentage of subjects with no new or newly enlarging lesions	45%	27%	
Number of Gd+ lesions at 2 years Mean (median) Percentage of subjects with 0 lesions 1 lesion 2 lesions 3 to 4 lesions 5 or more lesions Relative odds reduction (percentage)	0.1 (0) 93% 5% <1% 0 <1% 90%	1.8 (0) 62% 10% 8% 9% 11%	<0.0001
Mean number of new T1 hypointense lesions over 2 years	1.5	5.6	< 0.0001

Figure 1: Time to 12-Week Confirmed Progression of Disability (Study 1)



NOTE: Confirmed progression of disability is defined as at least 1.0 point increase on the EDSS from a baseline EDSS >= 1.0 confirmed for 12 weeks or at least 1.5 point increase on the EDSS from a baseline EDSS of 0 confirmed for 12 weeks.

Study 2: Placebo-Controlled Trial in RRMS

Study 2 was a 2-year multicenter, randomized, double-blind, placebo-controlled study that also included an open-label comparator arm in patients with RRMS. The primary endpoint was the annualized relapse rate at 2 years. Additional endpoints at 2 years included the number of new or newly enlarging T2 hyperintense lesions, number of T1 hypointense lesions, number of Gd+ lesions, proportion of patients relapsed, and time to confirmed disability progression as defined in Study 1.

Patients were randomized to receive TECFIDERA 240 mg twice a day (n=359), TECFIDERA 240 mg three times a day (n=345), an open-label comparator (n=350), or placebo (n=363) for up to 2 years. The median age was 37 years, median time since diagnosis was 3 years, and median EDSS score at baseline was 2.5. The median time on study drug for all treatment arms was 96 weeks. The percentages of patients who completed 96 weeks on study drug per treatment group were 70% for patients assigned to TECFIDERA 240 mg twice a day, 72% for patients assigned to TECFIDERA 240 mg three times a day and 64% for patients assigned to placebo groups.

TECFIDERA had a statistically significant effect on the relapse and MRI endpoints described above. There was no statistically significant effect on disability progression. The TECFIDERA 240 mg three times daily dose resulted in no additional benefit over the TECFIDERA 240 mg twice daily dose. The results for this study (240 mg twice a day vs. placebo) are shown in Table 3.

Table 3: Clinical and MRI Results of Study 2

	TECFIDERA 240 mg BID	Placebo	P-value
Clinical Endpoints	N=359	N=363	
Annualized relapse rate	0.224	0.401	<0.0001
Relative reduction	44%		
Proportion relapsing	29%	41%	0.0020
Relative risk reduction	34%		
Proportion with disability progression	13%	17%	0.25
Relative risk reduction	21%		
MRI Endpoints	N=147	N=144	
Mean number of new or newly enlarging T2 lesions over 2 years	5.1	17.4	<0.0001
Percentage of subjects with no new or newly enlarging lesions	27%	12%	
Number of Gd+ lesions at 2 years			
Mean (median)	0.5 (0.0)	2.0 (0.0)	
Percentage of subjects with			
0 lesions	80%	61%	
1 lesion	11%	17%	
2 lesions	3%	6%	
3 to 4 lesions	3%	2%	
5 or more lesions	3%	14%	
Relative odds reduction (percentage)	74%		<0.0001
Mean number of new T1 hypointense lesions over 2 years	3.0	7.0	<0.0001

16 HOW SUPPLIED/STORAGE AND HANDLING

TECFIDERA is available as hard gelatin delayed-release capsules in two strengths containing either 120 mg or 240 mg of dimethyl fumarate. The green and white 120 mg capsules are printed with “BG-12 120 mg” in black ink. The green 240 mg capsules are printed with “BG-12 240 mg” in black ink. TECFIDERA is available as follows:

30-day Starter Pack, (NDC 64406-007-03):

7-day bottle 120 mg capsules, quantity 14

23-day bottle 240 mg capsules, quantity 46

120 mg capsules:

7-day bottle of 14 capsules (NDC 64406-005-01)

240 mg capsules:

30-day bottle of 60 capsules (NDC 64406-006-02)

Store at 15°C to 30°C (59 to 86°F). Protect the capsules from light. Store in original container. Once opened, discard bottles of TECFIDERA after 90 days.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Dosage

Inform patients that they will be provided two strengths of TECFIDERA when starting treatment: 120 mg capsules for the 7 day starter dose and 240 mg capsules for the maintenance dose, both to be taken twice daily. Inform patients to swallow TECFIDERA capsules whole and intact. Inform patients to not crush, chew, or sprinkle capsule contents on food. Inform patients that TECFIDERA can be taken with or without food *[see Dosage and Administration (2.1)]*.

Anaphylaxis and Angioedema

Advise patients to discontinue TECFIDERA and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema *[see Warnings and Precautions (5.1)]*.

Progressive Multifocal Leukoencephalopathy

Inform patients that progressive multifocal leukoencephalopathy (PML) has occurred in a patient who received TECFIDERA. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes *[see Warnings and Precautions (5.2)]*.

Lymphocyte Counts

Inform patients that TECFIDERA may decrease lymphocyte counts. A blood test should be obtained before they start therapy. Blood tests are also recommended after 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*.

Flushing and Gastrointestinal (GI) Reactions

Flushing and GI reactions (abdominal pain, diarrhea, and nausea) are the most common reactions, especially at the initiation of therapy, and may decrease over time. Advise patients to contact their healthcare provider if they experience persistent and/or severe flushing or GI reactions. Advise patients experiencing flushing that taking TECFIDERA with food or taking a non-enteric coated aspirin prior to taking TECFIDERA may help *[see Adverse Reactions (6.1)]*.

Pregnancy and Pregnancy Registry

Instruct patients that if they are pregnant or plan to become pregnant while taking TECFIDERA they should inform their physician.

Encourage patients to enroll in the TECFIDERA Pregnancy Registry if they become pregnant while taking TECFIDERA. Advise patients to call 1-866-810-1462 or visit www.tecfiderapregnancyregistry.com for more information *[see Use in Specific Populations (8.1)]*.

41347-0X

Manufactured by:
Biogen Idec Inc.
Cambridge, MA 02142

Patient Information
TECFIDERA® (tek" fi de' rah**)**
(dimethyl fumarate) delayed-release capsules

What is TECFIDERA?

- TECFIDERA is a prescription medicine used to treat people with relapsing forms of multiple sclerosis (MS)
- It is not known if TECFIDERA is safe and effective in children under 18 years of age

Who should not take TECFIDERA?

- Do not use TECFIDERA if you have had an allergic reaction (such as welts, hives, swelling of the face, lips, mouth or tongue, or difficulty breathing) to TECFIDERA or any of its ingredients. See below for a complete list of ingredients.

Before taking and while you take TECFIDERA, tell your doctor if you have or have had:

- low white blood cell counts or an infection
- any other medical conditions

Tell your doctor if you are:

- pregnant or plan to become pregnant. It is not known if TECFIDERA will harm your unborn baby.
  - If you become pregnant while taking TECFIDERA, talk to your doctor about enrolling in the TECFIDERA Pregnancy Registry. You can enroll in this registry by calling 1-866-810-1462 or visiting www.tecfiderapregnancyregistry.com. The purpose of this registry is to monitor the health of you and your baby.
- breastfeeding or plan to breastfeed. It is not known if TECFIDERA passes into your breast milk. You and your doctor should decide if you will take TECFIDERA or breastfeed.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements

How should I take TECFIDERA?

- Take TECFIDERA exactly as your doctor tells you to take it
- The recommended starting dose is one 120 mg capsule taken by mouth 2 times a day for 7 days
- The recommended dose after 7 days is one 240 mg capsule taken by mouth 2 times a day
- TECFIDERA can be taken with or without food
- Swallow TECFIDERA whole. Do not crush, chew, or sprinkle capsule contents on food.
- Protect TECFIDERA from light. You can do this by storing the capsules in their original container. Throw away opened TECFIDERA after 90 days.

What are the possible side effects of TECFIDERA?

TECFIDERA may cause serious side effects including:

- **allergic reaction** (such as welts, hives, swelling of the face, lips, mouth or tongue, or difficulty breathing)
- **PML** a rare brain infection that usually leads to death or severe disability
- **decreases in your white blood cell count** Your doctor should do a blood test before you start treatment with TECFIDERA and while on therapy.

The most common side effects of TECFIDERA include:

- flushing, redness, itching, or rash
- nausea, vomiting, diarrhea, stomach pain, or indigestion
- Flushing and stomach problems are the most common reactions, especially at the start of therapy, and may decrease over time. Taking TECFIDERA with food may help reduce flushing. Call your doctor if you have any of these symptoms and they bother you or do

not go away. Ask your doctor if taking aspirin before taking TECFIDEA may reduce flushing.

These are not all the possible side effects of TECFIDERA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov.**

General Information about the safe and effective use of TECFIDERA

- Medicines are sometimes prescribed for purposes other than those listed in this Patient Information. Do not use TECFIDERA for a condition for which it was not prescribed. Do not give TECFIDERA to other people, even if they have the same symptoms that you have. It may harm them.
- If you would like more information, talk to your doctor or pharmacist. You can ask your doctor or pharmacist for information about TECFIDERA that is written for healthcare professionals.

What are the ingredients in TECFIDERA?

Active ingredient: dimethyl fumarate
Inactive ingredients: microcrystalline cellulose, silicified microcrystalline cellulose, croscarmellose sodium, talc, silica colloidal silicon dioxide, magnesium stearate, triethyl citrate, methacrylic acid copolymer - Type A, methacrylic acid copolymer dispersion, simethicone (30% emulsion), sodium lauryl sulphate, and polysorbate 80. **Capsule Shell:** gelatin, titanium dioxide, FD&C blue 1; brilliant blue FCF, yellow iron oxide and black iron oxide.

Manufactured by: Biogen Idec Inc., Cambridge, MA 02142, www.TECFIDERA.com or call 1-800-456-2255

This Patient Information has been approved by the U.S. Food and Drug Administration Issued: XX/xxxx

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204063/S-10

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA # Supplement #	204063/003
Applicant Name	Biogen Idec
Date of Submission	2/3/14
PDUFA Goal Date	12/3/14
Proprietary Name / Established (USAN) Name	Tecfidera/dimethyl fumarate
Dosage Forms / Strength	Oral delayed release capsules/120 mg, 240 mg
Proposed Indication(s)	Treatment of relapsing forms of multiple sclerosis
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jerry Boehm, MD
Statistical Review	N/A
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	N/A
Microbiology Review	N/A
Clinical Pharmacology Review	N/A
OPDP	N/A
OSI	N/A
CDTL Review	Sally Jo Yasuda, PharmD
OSE/DMEPA	N/A
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	N/A
PMHS	N/A
SEALD	N/A
Other	N/A

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Introduction

Tecfidera (dimethyl fumarate; DMF) is an approved drug product for the treatment of patients with relapsing forms of multiple sclerosis.

Biogen submitted the current supplemental application describing the effect of aspirin (ASA) pretreatment and slow dose titration on the flushing and gastrointestinal (GI) symptoms associated with the use of Tecfidera.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

Tecfidera was initially approved in 2013. The current marketed and labeled dose is 120 mg twice a day orally for 7 days followed by the maintenance dose of 240 mg twice a day orally.

Tecfidera causes flushing soon after initiation that generally resolves over time, but can be persistent in about a quarter of patients. Although rarely severe, it is common. The label notes that 40% of patients experienced flushing in clinical trials, with 3% discontinuing Tecfidera due to flushing and less than 1% with serious flushing symptoms that were not life-threatening but led to hospitalization.

Tecfidera also causes a GI constellation of nausea, vomiting, diarrhea, abdominal pain, and dyspepsia at a rate 2-6% greater than placebo in clinical trials.

In the original application, the sponsor presented the results of a descriptive study that suggested ASA pretreatment reduced flushing at the intended dose, with 3/6 pretreated patients experiencing flushing compared with 5/6 experiencing flushing without such treatment. (b) (4)

3. CMC/Device

N/A

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

N/A

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

N/A

8. Safety

The sponsor conducted study 109HV321, an 8-week, single-site, randomized, controlled, double-blind, safety and tolerability trial of Tecfidera 240 mg BID with or without ASA pretreatment, or by slow titration, conducted in 172 healthy subjects divided in 4 groups (placebo only, placebo and Tecfidera, ASA and Tecidera, and placebo and Tecfidera with slow titration). Subjects self-reported severity and impact scales for flushing and GI symptoms.

Dr. Boehm and Dr. Yasuda discuss the results of this study in detail in their reviews. I will not repeat the detailed numerical presentations contained in their reviews, but I will list the major findings:

- ASA pretreatment reduced the incidence of flushing (81% vs. 91%).
- ASA pretreatment reduced the number of flushing events (25 vs. 50).
- ASA pretreatment did not eliminate flushing (twice that in placebo).
- Slow titration did not reduce the incidence of flushing (98% vs 91%).
- ASA pretreatment reduced severity of flushing events (lower scores at all weeks).
- Slow titration did not affect severity of flushing events (scores mostly higher).
- ASA pretreatment did not clearly affect duration of flushing events (54 vs. 62 min).
- ASA pretreatment did not influence GI events (79% vs 81%).

The safety profile was consistent with that seen in the previous submission and described in approved labeling and is presented in detail in Dr. Boehm's review. Although there was no apparent toxicity associated with the use of ASA in this study, Dr. Boehm and Dr. Yasuda discuss the known risks associated with ASA use including bleeding, renal toxicity, and hepatic toxicity. Dr. Boehm suggests using the lowest effective dose to prevent flushing, and Dr. Yasuda recommends enhanced pharmacovigilance for bleeding and incorporating reporting of bleeding into the long-term postmarketing safety study of Tecfidera.

The sponsor has proposed [redacted] (b) (4)

(b) (4)

We will also include in this action updated labeling to address two other labeling supplements submitted by the sponsor to address the occurrence of hypersensitivity reactions and a new report of a single case of fatal progressive multifocal leukoencephalopathy (PML). Both have been reviewed in detail by Dr. Boehm. I agree with his findings. The PML case occurred in a patient participating in an extension trial of Tecfidera who had been taking the drug for 4 years and was severely lymphopenic for the majority of that time (3.5 years). This patient had no confounding history or concomitant medication use and the occurrence of PML appears to be plausibly related to the use of Tecfidera. The role of lymphopenia in the development of this case is uncertain. We have issued a Drug Safety Communication regarding this case and will describe it in labeling along with revised recommendations for lymphocyte monitoring.

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

N/A

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

The sponsor has provided acceptable evidence that ASA pretreatment (but not slow titration) reduces the incidence, severity, and number of flushing events. There are no safety concerns that preclude description of these findings in labeling.

I have discussed with Dr. Yasuda her recommendations for enhanced pharmacovigilance for bleeding and incorporation of reporting of bleeding into the long-term postmarketing safety study of Tecfidera. After discussion, she and I both agree that that any severe bleeding episodes will be brought to our attention through routine safety reporting. We will discuss with the sponsor the need to remain vigilant for ASA-related events in the long-term postmarketing safety study of Tecfidera.

We have agreed with the sponsor on product labeling that includes a description of ASA pretreatment for flushing, updated hypersensitivity reaction information, and a description of the first reported case of PML with Tecfidera.

For these reasons, I will issue an approval letter for this supplemental NDA, to include the agreed-upon product labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
12/03/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204063/S-10

OTHER REVIEW(S)

CLINICAL SAFETY REVIEW

NDA number	204-063
Application holder	Biogen Idec, Inc.
US product trade name(s)	Tecfidera
Product established name	Dimethyl Fumarate
Date of first US approval	3/27/13
US approved indications	TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis
Material Reviewed	Safety Report, 10/24/14, Labeling proposal 10/29/14, Labeling Supplement 10 11/6/14, 11/7/14, 11/25/14, 11/26/14
Medical reviewer and Office/Division	Gerard Boehm, MD, MPH ODE 1/DNP

On 10/20/14, Biogen informed the Division of the first confirmed case of progressive multifocal leukoencephalopathy (PML) in a patient treated with Tecfidera. The case involved a 54 year old female with a history of multiple sclerosis (MS) since 1996. She received no MS treatment from 1996-2005. From 2005-2008 she was treated with Copaxone and in mid-2008 she experienced MS relapses. In 2008, the patient enrolled in Tecfidera randomized controlled trial (RCT) 109-MS-301 and received placebo treatment. After completing the RCT in 2010, the patient was enrolled in the extension trial 109-MS-303, where she received Tecfidera. During this trial, she experienced persistent lymphopenia but her MS was considered stable. She received Tecfidera in this trial for 4 years. In (b) (6) she experienced worsening neurological symptoms. She was hospitalized and treated for MS relapses with minimal clinical improvement. Treatment included intravenous corticosteroids and plasmapharesis. Her clinical course deteriorated and she became quadriplegic, and unable to speak. She developed aspiration pneumonia due to dysphagia and died. A CSF sample was positive for JC viral DNA. Neither brain biopsy, nor post-mortem exam was performed. Additional clinical details are provided as Appendix 1 to this review.

PML

PML is a is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Patients at risk for PML include those with hematologic malignant neoplasms, HIV, iatrogenic immune suppression (ex. organ transplant patients), and patients treated with select monoclonal antibodies (ex. natalizumab, rituximab, efalizumab), or with other drugs that effect the immune system. In some cases, the underlying predisposing factors for PML are unclear. In a publication by Gheuens et al[1], the authors described 38 cases (5 of their own, 33 from the medical literature) of PML in patients with minimal or occult immunosuppression. The authors identified several cases with no specific underlying diagnosis, in

[1] Gheuens S, Pierone G, Peeters P, Koralnik IJ. Progressive multifocal leukoencephalopathy in individuals with minimal or occult immunosuppression. J Neurol Neurosurg Psychiatry. 2010 March; 81 (3): 247-254.

addition to cases with underlying conditions such as cirrhosis, renal failure, and idiopathic CD4+ lymphocytopenia.

Symptoms associated with PML are diverse, and may include behavioral and cognitive symptoms, motor weakness, gait abnormalities, visual field deficits, speech and language disturbances, and incoordination. Clinical and imaging manifestation consistent with PML along with the finding of JC virus in CSF is considered diagnostic.[2]

Cases of PML/Opportunistic Infections with Tecfidera
At the time of the NDA review, no cases of PML or opportunistic infections were identified in Tecfidera exposed patients in the clinical trial population. Biogen confirmed that the above described case is the first confirmed case of PML with Tecfidera.

Tecfidera clinical trial exposure
Biogen noted in the CIOMS report of the PML case that 4,057 subjects have been exposed to Tecfidera in clinical trials. At the time of the PML case, Biogen reported the following MS clinical trial exposure to Tecfidera:

Exposure to BG00012 ≥ 6 months:	n= 2,099
Exposure to BG00012 ≥ 1 year:	n= 1,869
Exposure to BG00012 ≥ 2 years:	n= 1,602
Exposure to BG00012 ≥ 4 years:	n= 1,001

Tecfidera Post Marketing Use
Biogen estimated that worldwide approximately (b) (4) patients have been exposed to Tecfidera in the post marketing period. Tecfidera was approved by FDA on 3/27/13 (International birth date).

Fumaderm
Biogen noted that Fumaderm, a drug that contains dimethyl fumarate in combination with 3 different salts of monoethyl fumarate, was approved in 1994 in Germany for the treatment of moderate and severe psoriasis.

Fumaderm and PML
Biogen examined the Fumaderm safety database for opportunistic infections and identified occasional reports of such cases. Biogen noted that there have been 3 cases of PML reported with Fumaderm. Biogen felt that Fumaderm was not involved in one case because the onset of PML was within 1 month of starting Fumaderm. In this case, Biogen felt PML was more likely related to underlying sarcoidosis requiring treatment with steroids and methotrexate. In a second case, Biogen identified potential

[2] Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, Bartt R, Major EO, Nath A. PML diagnostic criteria: Consensus statement from the AAN Neuroinfectious disease section. Neurology 2013;80;1430-1438.

confounding factors such as prior treatment with efalizumab, history of melanoma, and decreased immunoglobulins of unknown etiology. In the 3rd case, a 74 year old male was diagnosed with PML after 3 years of Fumaderm treatment, which included decreased lymphocyte counts <500 for over 2 years. This patient had previously been treated for psoriasis with acitretine (an aromatic retinoid) and methotrexate. Biogen felt that this single case of PML without confounding factors in (b) (4) person years of use was consistent with the background rate of PML in patients with autoimmune diseases. In addition to PML, Biogen identified one report of tuberculosis and one of Kaposi sarcoma in their database.

PML and compounded fumarate product

In addition to the Fumaderm PML cases described above, Biogen provided information about a PML case that occurred in a Psoriasis patient treated with compounded dimethyl fumarate and copper monoethyl fumarate. This event occurred in a 42 year old female from the Netherlands who was treated with dimethyl fumarate and copper monoethyl fumarate for 6-7 years. She had lymphopenia (lymphocyte count 200). Biogen noted that if no confounding factors are identified for this case, then it is possible that compounded fumarate had a contributory role in the development of PML, in the setting of severe lymphopenia.

Biogen proposed labeling changes

Biogen's labeling changes included edits to the Warnings and Precautions section for lymphopenia and mention of the PML case in a newly created Post Marketing Experience section. Biogen's proposal would include a (b) (4) (b) (4) I include Biogen's labeling change proposal as Appendix 2 to this review.

Biogen justification for their proposed labeling changes

Biogen provided a document that explained their reasoning regarding their proposed labeling changes for Tecfidera.

Biogen identified a number of treatments associated with PML including natalizumab, efalizumab, rituximab, mycophenolate mofetil, and brentuximab vedotin, cytoxic chemotherapeutic drugs, fludarabine, cyclophosphamide, methotrexate, and corticosteroids. Biogen noted that some of these agents are associated with lymphopenia. In addition, Biogen noted that other disease states are associated with lymphopenia and PML including HIV, autoimmune rheumatic diseases (ARD), and idiopathic CD4+ lymphocytopenia (ICL). Biogen notes that healthy adults can have transient, reversible lymphopenia or persistent and stable lymphopenia not associated with clinical findings. Biogen therefore concludes that it must be severe, prolonged lymphopenia that increases PML risk.

Biogen discussed the PML cases with Fumaderm and compounded fumarates. In addition to the four cases above, Biogen identified 3 more cases. One case had limited information and was unevaluable.

The other 2 cases were confounded (underlying myelodysplastic syndrome, underlying autoimmune hepatitis, SLE, and previous treatment with steroids and cyclophosphamide). Despite confounding factors in some cases, Biogen noted that 5 cases had lymphopenia of at least 2 years. Biogen concluded that "severe, prolonged lymphopenia (<500 cells/uL for $\geq$2 years) appears to be a risk factor for the development of PML in the setting of treatment with other fumarates."

Biogen presented results from additional lab analyses from Tecfidera trials. Biogen reported that 7% of subjects treated with Tecfidera in the Phase 2 and 3 controlled and uncontrolled studies of Tecfidera in MS had at least 1 postbaseline lymphocyte count <500 cells/uL. Thirty-nine percent of these subjects had just a single occurrence of a post-baseline lymphocyte count <500 cells/ μ L. Two percent (47 of 2470 subjects) of subjects had post-baseline lymphocyte counts <500 cells/ μ L for at least 6 months. Furthermore, Biogen reported that "within this subset, lymphocyte counts tended to remain at approximately this level with continued therapy, some for 3.5 years or more." Within the 2% with lymphocyte counts <500 cells/ μ L for at least 6 months, 10 (21%) had their first lymphocyte count <500 cells/ μ L by 6 months, 31 (66%) had their first count <500 cells/ μ L by 12 months; the remaining 6 subjects presented after 12 months.

Biogen also presented information about lymphocyte recovery after stopping Tecfidera, although there were few subjects in this analysis group. Among the 47 subjects with lymphocyte counts <500 cells/ μ L for at least 6 months, 9 patients discontinued or completed the study. Of the 9 subjects, 8 had lymphocyte counts at least 1 month after their final dose. All 8 subjects showed increases in lymphocyte counts following their final dose of BG00012. The plot that Biogen provided for these patients demonstrates improvement, but not complete recovery to normal.

Discussion

Biogen reported the first confirmed case of PML in a patient treated with Tecfidera. This clinical trial patient had no identified alternative explanation for development of PML (i.e., underlying immunocompromised-related disease, use of another medication which increases the risk for PML, etc.). The patient did have prolonged lymphopenia, a known potential side effect of Tecfidera. Six evaluable cases of PML, 2 without identified confounding factors, have been reported with Fumaderm (contains dimethyl fumarate) and a compounded fumarate preparation. Many of these cases also involved lymphopenia.

The Tecfidera patient who experienced PML was enrolled in an extension trial at the time of diagnosis. This is the first confirmed case among the approximately 4,000 exposed clinical trials patients. Given that this case occurred following 4 years of treatment, there is the possibility that the risk for PML is not uniform over time, and may increase with duration of treatment. Given that Tecfidera has only been approved for 20 months, it will be important to monitor for new reports of PML in the coming months, as post marketing exposure duration increases.

The precise causal relationship between Tecfidera and PML is not understood at this time. As noted above, the patient with PML described in the report experienced prolonged lymphopenia. It would be premature to conclude that lymphopenia is the only explanation for PML risk with Tecfidera, based on this single case. Even if one accepts that the Fumaderm cases inform about PML risk and Tecfidera, (b) there are still too few unconfounded cases to allow for firm conclusions regarding causal mechanism.

(b) (4) . Biogen identified a number of treatments that are associated with lymphopenia and increased PML risk, but also identified treatments that increase PML risk without causing lymphopenia. Biogen identified disease states that are associated with both lymphopenia and PML (ex. HIV), but publications that they cited raised questions about the role of lymphopenia in increasing PML risk for other diseases. The publication by Carson et al[3] supports Biogen's position regarding lymphopenia and PML by noting "CD4+ and CD8+ T lymphopenia, resulting from HIV infection, chemotherapy, or immunosuppressive therapy, are the primary risk factors". Two additional publications suggest the role of factors other than lymphopenia in PML risk. In the publication by Jamilloux et at[4] that Biogen cited, the authors wrote the following, "Thereby, sarcoidosis associated PML cannot be attributed to immunosuppressive medications or CD4 lymphocytopenia only, suggesting more complex underlying mechanisms." From a publication on lupus and PML that Biogen cited, Molloy and Calabrese[5] wrote the following, "No clear mechanism has yet been elucidated for this putative increased risk of PML among SLE patients. While lymphopenia is common among patients with SLE and is related to the disease itself and/or the immunosuppressive therapy, it is neither necessary nor sufficient for the development of PML.

Strengthening the Tecfidera Warnings and Precautions statement regarding monitoring recommendations for lymphopenia seems appropriate. Increased monitoring as proposed by Biogen, should identify patients with prolonged, severe lymphopenia. Given our current incomplete understanding regarding lymphopenia and PML risk in Tecfidera patients described above, it is not clear if increased lymphocyte monitoring with recommendations for interruption/discontinuation in patients with persistent lymphopenia will mitigate PML risk.

Recommendations

[3] Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events Reports (RADAR) Project. Lancet Oncol. 2009;10(8):816-24.

[4] Jamilloux Y, Néel A, Lecouffe-Desprets M, et al. Progressive multifocal leukoencephalopathy in patients with sarcoidosis. Neurology. 2014;82(15):1307-13.

[5] Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy associated with immunosuppressive therapy in rheumatic diseases: evolving role of biologic therapies. Arthritis Rheum. 2012;64(9):3043-51.

The Agency is undertaking a communication effort (Drug Safety Communication) to promptly inform prescribers and patients of the case of PML.

The Division is requesting that Biogen add information about this PML case to labeling. Biogen provided a labeling proposal that would increase lymphocyte monitoring recommendations in the Warnings and Precautions statement on lymphopenia that is currently in labeling, and would add information about the PML case (b) (4). The proposals to increase lymphocyte monitoring appear appropriate and will be included, with edits, in labeling. Although this is the first identified PML case with TECFIDERA, the seriousness of PML supports prominent placement in labeling. I recommend adding a Warnings and Precautions statement. Given that this is the first case, (b) (4)

(b) (4)

The Division should adopt the increased lymphocyte monitoring recommendations proposed by Biogen.

Addendum

In a Division meeting on 11/4/14, the review team discussed the labeling proposal. The Division decided to include the information about the PML case as section 5.2, and move information about lymphopenia to section 5.3. Information about PML will also be included in section 17 of labeling (Information for patients) as well as the patient information handout. The Division agreed to labeling language with Biogen during a 12/2/14 conference call.

Appendix 1- Details from the case report of PML

Clinical trial patient (109-MS-303 370-302) from Germany

History
54 year old female with a history of MS (1996), muscle spasms, and hypertension
Mid-2008 suffered multiple MS relapses with "significant progress" on MRIs
Last cortisol treatment was 5 years ago (prior to 2008?)
No history of autoimmune disorders

Enrolled in BG12 RCT 109-MS-301 and then rolled over into 109-MS-303
Treatment dates 2/12/2010-7/15/14 (onset of symptoms); BG-12 stopped 8/23/14
During the preceding RCT 109-MS-301, where the patient received Placebo, her lymphocyte counts were normal and ranged from 1.72-2.32 (0.91-4.28)
During trial 109-MS-303, the patient had persistent lymphopenia considered not clinically significant

Lymphocytes

5/10/10	0.84
7/29/10	0.80
10/21/10	0.63
1/20/11	0.45

For the remainder of the trial, lymphocytes ranged from 0.29 (2/7/13) to 0.53 (9/22/11 and 4/9/14).

Concomitant medications: Ramipril, hydrochlorothiazide, bisoprolol, baclofen, dalfampridine.
On no MS therapies from 1996-2005
Treated with Copaxone 12/05-1/08
No history of Tysabri, Gilenya, or immunosuppressant medications.

Event summary
MS "stable" until the summer of 2014

(b) (6) First symptoms of deterioration (not described).

On (b) (6) the patient was hospitalized (or remained an outpatient) for MS relapse and treated with IV methylprednisolone 1000mg for 3 days. Patient experienced further deterioration, difficulty walking.

On (b) (6) she was hospitalized for severe exacerbation of MS. Symptoms began 2 weeks prior to admission and included gait disorder, speech disorder, and coordination disturbance affecting her left arm. EDSS on admission was 5.0.

Neuro exam: Cranial nerves were without findings. Deviation in arm extension test on the left, down-drift in legs extension test on both sides, spastic hypertonia of both legs more pronounced on the left,

Babinski negative on both sides, ataxic pointing test on the left, bradydiadochokinesia on the left, no aphasia, moderate dysarthria, uncertain ataxic stance and gait.

Labs:
leukocytes 10.5/nL (3.5-9.8)
neutrophils 9.1/nL (1.6-7.1)
lymphocytes 0.4/nL (1-2.9)
eosinophils 0.03/nL (0.06-0.46)
monocytes 0.9/nL (0.2-0.6)

MRI on (b) (6)
supra- and intracerebral lesions, multiple lesions on the cervical spine cord, and a moderately hypotrophic cervical spinal cord Update: a brain and cervical spine MRI with contrast agent (no previous examination for comparison) found significant dilatation of inner and outer cerebrospinal fluid spaces due to generalized volume reduction supra- and infratentorial. In T2w and FLAIR – hyperintense spotty and finger-shaped confluent lesions associated with corpus callosum in the peri- and supraventricular white matter on both sides more pronounced on the left. Lesions in corona radiata and in capsula interna on both sides. In T2w -spotty hyperintense lesions with unsharp-edged contours also in the left cerebellar hemisphere adjacent to superior cerebellar peduncle, in mesencephalon, in pons and in medulla. No diffusion disturbances seen in DWI. No contrast enhancement, no evidence of floridity. Cervical spine: There were hyperintense spotty signal changes intramedullary centrally in the whole cervical myelon seen in T2w. No contrast enhancement. In conclusion, findings were consistent with MS including distinct supra- and infratentorial lesion load and multiple demyelination lesions also in the cervical spine (maximum C5 centrally and more pronounced on the right).

Treatment (b) (6)
Prednisolone 2000mg IV QD

(b) (6) lab values were “normal” except for elevated leukocytes (13.3/nL).

(b) (6) BG12 stopped

(b) (6) leukocytes 6.3/nL

(b) (6) (unspecified date) she tested positive for JCV antibodies.

(b) (6) she was discharged to rehabilitation clinic with “only slight improvement”. The report noted that the patient had persisting severe gait disorder, left arm weakness, and difficulty speaking.

(b) (6) Rehabilitation facility
On admission, she was unable to stand, had speech difficulties, and tingling sensation of left hand and mouth.

Neuro exam: horizontal nystagmus when looking to the left, moderate dysarthria, spastic hypertonia of both legs more pronounced on the left, legs extension test not possible, no pyramidal tract signs, pointing test dysmetric, bradydiadochokinesia on the left, uncertain standing, walking with rollator possible for approximately 6 m.

(b) (6) was able to walk 7.62m during 35 seconds, started on dalfampridine
She developed severe dizziness, was unable to walk, and physiotherapy was discontinued.

(b) (6) readmitted to a hospital for worsening MS relapse (EDSS 7.0).

(b) (6) she received Prednisolone 1000mg/day x2days

(b) (6) leukocytes 5.9/nL, neutrophils 5.7/nL, lymphocytes 0.2/nL, eosinophils 0.0/nL, monocytes 0.1/nL

(b) (6) MRI with contrast agent was performed and compared with the previous examination from (b) (6) there were known signal enhancements in the corpus callosum and small defects in radiatio of corpus callosum. These lesions remained unchanged. The known signal enhancement in left cerebellar peduncle increased. Significant increasing of signal changes in the pons, more pronounced on the left. Newly occurred signal enhancements cerebellar on the right side reaching up to the right cerebellar peduncle. No BBB (blood brain barrier) disturbance. There was less pronounced diffusion disturbance seen in the area of right cerebellar lesions reaching up to the right cerebellar peduncle. No contrast enhancement. In conclusion, newly occurred distinct signal alterations in the pons more pronounced on the left and in the cerebellum on both sides reaching up to right cerebellar peduncle and was considered to be most probably consistent with MS.

(b) (6)- persistent lymphopenia (0.2/nL). Hepatitis A virus IgG positive, Hepatitis A virus IgM negative, Hepatitis B virus surface negative, Hepatitis B virus surface 47 U/L (greater than 10) [discrepant information], Hepatitis B virus core negative, Hepatitis C virus-Ab negative, and HIV 1,2 negative

(b) (6) a brain MRI with contrast agent found a different image impression due to considerable motion artifacts. Compared with the previous examination from (b) (4), especially in T2w sequences known signal alterations in the pons and in the cerebellum significantly increased accompanied by distinct diffusion disturbance and corresponding signal attenuation in T1w. Ascending signal changes up to mesencephalon. Compared to previous examination, there was also increasing diffusion disturbance parietal on the left and newly occurred diffusion disturbance occipital with progressing edema-signal there. No contrast enhancement. In conclusion, there was significant progress especially in the pons and in the cerebellum as well as subcortical occipital and parietal on the left side.

Labs: Borrellia IgG was negative (less than 16 RE/mL), Borrelia IgM negative (less than 16 RE/mL). JC Virus DNA (liquor) positive ca. (circa) 10,000 geq/mL. On an unspecified date in (b) (6), the liquor sample from (b) (6) was retested for JC Virus DNA and results were positive ca. 2,500 geq/mL.

Underwent 5 courses of plasmapharesis during the hospitalization

(b) (6) CSF (LP on (b) (4)) showed a high JCV DNA level (10,000 geq/mL) and a final diagnosis of PML was made on an unspecified date.
Subject was quadriplegic, mutistic, "nearly locked-in", developed aspiration pneumonia due to massive dysphagia and died on (b) (6) at 05:00. Autopsy refused by family.

2 page(s) of Draft labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GERARD A BOEHM
12/03/2014

SALLY U YASUDA
12/03/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 204063/S-10

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, January 20, 2015 7:33 AM
To: 'Tammy Phinney'
Subject: RE: Follow up on DHCP letter
Attachments: Comments for sponsor tecfidera dhcp letter 1 16 15.doc

Tammy

Please see the attached Word doc for the Division's comments regarding the DHCP letter submitted for Tecfidera.

Best Regards,
Laurie

-----Original Message-----
From: Tammy Phinney [mailto:tammy.phinney@biogenidec.com]
Sent: Monday, January 05, 2015 10:06 AM
To: Kelley, Laurie
Subject: Re: Follow up on DHCP letter

Great. Thank you.

Sent from my iPhone

> On Jan 5, 2015, at 10:05 AM, "Kelley, Laurie" <Laurie.Kelley@fda.hhs.gov> wrote:
>
> Tammy
>
> The DHCP letter is currently being reviewed by the safety team. I will follow up with them to see when we will have any comments for you.
>
> Laurie
>
> ----- Original Message -----
> From: Tammy Phinney [mailto:tammy.phinney@biogenidec.com]
> Sent: Monday, January 05, 2015 10:02 AM
> To: Kelley, Laurie
> Subject: Follow up on DHCP letter
>
> Happy New Year Laurie!
> I hope you had a nice holiday and maybe enjoyed a few days off. We actually flew to the Caribbean Christmas Day so we enjoyed some sun and warmth. Now I'm freezing!

>
> I wanted to touch base with you about the Tecfidera DHCP letter we submitted on December. We haven't heard back and I was wondering if Dr Dunn believes it is necessary for us to disseminate given the safety alert issued by the Agency and the publicity that the event generated. Could you let us know the Agency's thinking on this?
>
> Thank you
> Tammy
>
> Sent from my iPhone
>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURIE A KELLEY
01/20/2015