

Instructions for Healthcare Providers

To prescribe TECFIDERA, please follow these steps:

- 1 After discussing TECFIDERA with your patient, have your patient read the Patient Consent Information, and request that the patient sign the indicated areas on the accompanying Start Form.**

Biogen takes your patient's confidentiality very seriously. While patients are not required to sign the Start Form in order to receive TECFIDERA, signing both lines will expedite their enrollment in Biogen support services, such as the QuickStart and **\$0 Copay programs** (call 1-800-456-2255 for eligibility guidelines). In addition, with both signatures Biogen will have access to your patient's prescription status should you or your patient need assistance.

- 2 Complete the rest of the Start Form.**

Copy both sides of the patient's medical insurance card and pharmacy benefit card, if available. In some cases, the medical and pharmacy cards may be the same.

- 3 Give your patient the Instructions for Patients and Patient Consent Information pages.**

Then, fax the start form to 1-855-474-3067. Prescriptions are only valid when received via fax.

Your patient will be contacted by a pharmacy in the TECFIDERA Pharmacy Network to arrange for delivery of the prescription.

Please be sure to fill out all of the sections of the Start Form. Incomplete areas may delay the start of treatment.

If you have any questions or want to learn more about TECFIDERA, please call 1-800-456-2255 or visit TECFIDERAHCP.com.

Please see last page and Full [Prescribing Information](#) and [Patient Information](#) for Important Safety Information. This file is an electronic PDF from TECFIDERA.com or TECFIDERAHCP.com.



225 Binney Street
Cambridge, MA 02142
(800) 456-2255
Tecfidera.com

Instructions for Patients

How do I get started?

- 1 Read the Patient Consent Information and sign as indicated in the shaded area of the Start Form.**
This will enable you to enroll in Biogen support services, such as the QuickStart and **\$0 Copay programs** (call 1-800-456-2255 for eligibility guidelines).
- 2 Be sure to include your e-mail address in the space provided.**
By giving us your e-mail address, you can stay up-to-date on the latest news about TECFIDERA.
- 3 Your doctor fills out the rest of the Start Form.**
You're done. Your doctor will fax us the Start Form.

What happens next?

- You can expect to receive several important phone calls. These calls will come from a Biogen support coordinator and a TECFIDERA pharmacy.
 - You'll see either 919-993-7000, a 1-800 number, or "unknown" on your caller ID. **Please be sure to answer when you see these calls.** They are intended to aid you in getting started on TECFIDERA as smoothly and quickly as possible.
- Your prescription can be shipped directly to your home.

If you have any questions or want to learn more about TECFIDERA, please call 1-800-456-2255 or visit TECFIDERA.com.

Indication

Tecfidera® (dimethyl fumarate) is a prescription medicine used to treat people with relapsing forms of multiple sclerosis.

Important Safety Information

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.

Before taking and while you take TECFIDERA, tell your doctor about any low white blood cell counts or infections or any other medical conditions.

What are the possible side effects of TECFIDERA?

TECFIDERA may cause serious side effects including:

- Allergic reactions**
- PML, which is a rare brain infection that usually leads to death or severe disability.**
- Decreases in your white blood cell count.** Your doctor should check your white blood cell count before you take TECFIDERA and from time to time during treatment
- Liver problems.** Your doctor should do blood tests to check your liver function before you start taking TECFIDERA and during treatment if needed. Tell your doctor right away if you get any symptoms of a liver problem during treatment, including:

- severe tiredness
- loss of appetite
- pain on the right side of your stomach
- dark or brown (tea color) urine
- yellowing of your skin or the white part of your eyes

The most common side effects of TECFIDERA include flushing and stomach problems. These can happen especially at the start of treatment and may decrease over time. Taking TECFIDERA with food may help reduce flushing. Call your doctor if these symptoms bother you or do not go away. Ask your doctor if taking aspirin before taking TECFIDERA 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 daily.med.nlm.nih.gov.

Tell your doctor if you are pregnant or plan to become pregnant, or breastfeeding or plan to breastfeed. It is not known if TECFIDERA will harm your unborn baby or if it passes into your breast milk. Also tell your doctor if you are taking prescription or over-the-counter medicines, vitamins, or herbal supplements. If you take too much TECFIDERA, call your doctor or go to the nearest hospital emergency room right away.

For additional Important Safety Information, please see enclosed full Prescribing Information and Patient Information. This is not intended to replace discussions with your doctor.

Please read the following. If you agree, sign and date the corresponding section on the following page.

I. Authorization to Share Health Information

By signing this Authorization, I authorize my healthcare provider, my health insurance company, and my pharmacy providers ("Healthcare Entities") to disclose to Biogen, and companies working with Biogen (collectively, "Biogen"), health information relating to my medical condition, treatment, and insurance coverage for Biogen to provide me with (i) support services (and related information and materials) related to any of Biogen products, including but not limited to, online support, financial assistance services, compliance and persistency and other therapy support services, (ii) conduct data analytics, market research and other internal business activities, and (iii) information about Biogen products, services, and programs and other topics of interest for marketing, educational or other purposes. Once my health information has been disclosed to Biogen, I understand that federal privacy laws no longer protect the information. However, Biogen agrees to protect my health information by using and disclosing it only for purposes authorized in this Authorization or as required by law or regulations. I understand that my pharmacy provider may receive remuneration from Biogen in exchange for the health information and/or for any therapy support services provided to me.

I understand that I may refuse to sign this Authorization. I further understand that my treatment (including with a Biogen product), payment for treatment, insurance enrollment or eligibility for insurance benefits are not conditioned upon my agreement to sign this Authorization; but if I do not sign it or later cancel it, I will not be able to receive Biogen therapy support services.

I may cancel this Authorization at any time by mailing a letter to: Biogen, 5000 Davis Drive, PO Box 13919, Research Triangle Park, NC, 27709 or visiting biogen.com/privacy. Canceling this Authorization will end my consent to further disclosure of my health information to Biogen by my Healthcare Entities after they are notified of my cancellation, but will not affect previous disclosures by them pursuant to this Authorization. Canceling this authorization will not affect my ability to receive treatment, payment for treatment, or my eligibility for health insurance.

This Authorization expires ten (10) years, or such shorter timeframe required by applicable law, from the day I sign it as indicated by the date next to my signature unless otherwise canceled earlier as set forth above.

Please sign in the space in Section **A on the following page to authorize your consent.**

II. Patient Services and Marketing/Other Communications Authorization

Patient Services

I authorize Biogen, and companies working with Biogen, to provide me with support services related to any of Biogen products, including but not limited to: online support, financial assistance services, compliance and persistency and other therapy support services, as well as any information or materials related to such services. I agree and authorize that any nurse providing such support services is not employed by my healthcare professional. I authorize Biogen, and companies working with Biogen, to contact me to provide such services and information by mail, e-mail, fax, telephone call, text message (including calls and text messages made with an automatic telephone dialing system or a prerecorded voice), and other mutually agreed upon means. I also authorize Biogen, and companies working with Biogen, to use my health information in connection with the services, including, without limitation, sharing such information with my healthcare provider, insurance provider, or pharmacy. I also authorize the disclosure of my health information to specific individuals that I have designated.

Marketing/Other Communications

I further authorize Biogen, and companies working with Biogen, to contact me by mail, email, fax, telephone call, and text message for marketing purposes or otherwise provide me with information about Biogen products, services, and programs or other topics of interest, conduct market research or otherwise ask me about my experience with or thoughts about such topics. I understand and agree that any information that I provide may be used by Biogen to help develop new products, services, and programs. Note that Biogen will not sell or transfer your personal data to any unrelated third party for marketing purposes without your express permission. I understand that I may revoke this authorization and choose not to receive services or information from Biogen by mailing a letter to the address above or visiting biogen.com/privacy.

Please sign in the space in Section **B on the following page to authorize your consent.**

III. Opt-in for Automated Marketing Calls and Text Messages

I also consent to receive autodialed and prerecorded marketing calls and text messages from Biogen, and companies working with Biogen, at the telephone number(s) that I provide. I understand that my consent is not required as a condition of purchasing or receiving any goods or services from Biogen. I understand that I may revoke this authorization and choose not to receive automated marketing calls and text messages from Biogen by mailing a letter to the address above or visiting biogen.com/privacy.

Please check the box on Section **C on the following page to authorize your consent.**

I. Authorization to Share Health Information

I have read and understand the Authorization to Share Health Information and agree to the terms.

A Signature of patient or patient representative Date If signed by patient representative, please explain authority to act on behalf of the patient:

II. Patient Services and Marketing/Other Communications Authorization

I have read and understand the Patient Services and Marketing/Other Communications Authorization and agree to the terms.

B Signature of patient or patient representative Date In addition, I authorize the disclosure of my health information to the following designated individual(s) (optional): Designated individual (print name) Relationship

III. Marketing Opt-in

C I have read and understand Opt-In to Receive Marketing Communications and hereby agree to receive information from Biogen (optional).

Patient Information

Male Female First name Last name Address City State Zip Date of birth Email address Home phone Cell phone Preferred number OK to leave message Best time to reach me: Morning Afternoon Evening Patient preferred specialty pharmacy

THE FOLLOWING INFORMATION SHOULD BE FILLED OUT BY YOUR HEALTHCARE PROVIDER

Prescription for TECFIDERA

Month 1 Titration Starter Pack Rx for TECFIDERA: 120mg PO BID x7 days #14 capsules 240mg PO BID x23 days #46 capsules No refills Months 2-13 Maintenance Rx for TECFIDERA: 240mg PO BID x90 days #180 capsules 3 refills 240mg PO BID x30 days #60 capsules 11 refills Special instructions:

QuickStart Program

(Optional at no cost; for commercially insured patients only)

In the event there is a delay in securing prescription coverage, I authorize Biogen to forward this prescription to the QuickStart Program designated pharmacy in order to dispense TECFIDERA directly to the above named patient. TECFIDERA Patient Services will notify the patient via telephone prior to each QuickStart shipment. Both patient signatures above are needed to expedite enrollment in the QuickStart Program.

QuickStart Rx for TECFIDERA: Titration Rx 120mg PO BID x7 days #14 capsules 240mg PO BID x7 days #14 capsules Maintenance Rx 240mg PO BID x14 days #28 capsules 10 refills

Medical Benefit Information

Primary insurance Policy # Group # Insurance company phone Policyholder first name Policyholder last name

Pharmacy Benefit Information

Attach copies of both sides of patient's pharmacy benefit card(s).

Check if no coverage Check if patient has secondary insurance Patient preferred specialty pharmacy

Statement of medical necessity

Primary diagnosis: ICD 10: G35 Current or most recent therapy Dates/Duration Other therapy No prior disease modifying therapies

Prescriber information

First name Last name Address City State Zip Phone Fax NPI # Tax ID # Clinical/Hospital affiliation Office contact name Best time to contact: Morning Afternoon

Prescriber Authorization*

I authorize Biogen as my designated agent and on behalf of my patient to (1) forward the above statement of medical necessity and furnish any information on this form to the insurer of the above-named patient and (2) forward the above prescription, by fax or other mode of delivery, to the pharmacy chosen by the above-named patient. I certify that the rationale for prescribing TECFIDERA therapy is for a primary diagnosis of ICD-10: G35, and I will be supervising the patient's treatment accordingly.

Prescriber signature (Dispense as Written) Date

Prescriber signature (Substitution Permitted) Date Signature stamps not acceptable.

*In New York, please attach copies of all prescriptions on Official New York State Prescription forms.

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, Blood Tests Prior to Initiation of Therapy (2.2)	1/2017
Warnings and Precautions, PML (5.2)	2/2016
Warnings and Precautions, Liver Injury (5.4)	1/2017

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 $<0.5 \times 10^9/L$ persist for more than six months. (5.3)
- Liver injury: Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiating TECFIDERA and during treatment, as clinically indicated. Discontinue TECFIDERA if clinically significant liver injury induced by TECFIDERA is suspected. (5.4)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Biogen 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: 1/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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*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. 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)*].

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.

2.2 Blood Tests 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)*].

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with TECFIDERA [*see Warnings and Precautions (5.4)*].

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

Progressive multifocal leukoencephalopathy (PML) has occurred in patients with MS treated with TECFIDERA. 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. A fatal case of PML occurred in a patient who received TECFIDERA for 4 years while enrolled in a clinical trial. During the clinical trial, the patient experienced prolonged lymphopenia (lymphocyte counts predominantly $<0.5 \times 10^9/L$ for 3.5 years) while taking TECFIDERA [see *Warnings and Precautions (5.3)*]. 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.

PML has also occurred in the postmarketing setting in the presence of lymphopenia ($<0.8 \times 10^9/L$) persisting for more than 6 months. While the role of lymphopenia in these cases is uncertain, the majority of cases occurred in patients with lymphocyte counts $<0.5 \times 10^9/L$.

At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. 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 $<0.5 \times 10^9/L$ (lower limit of

normal $0.91 \times 10^9/L$). 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 $<0.8 \times 10^9/L$ or $\leq 0.5 \times 10^9/L$ in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly $<0.5 \times 10^9/L$ 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, and in this group the majority of lymphocyte counts remained $<0.5 \times 10^9/L$ with continued therapy. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

Obtain a CBC, including lymphocyte count, before initiating treatment with TECFIDERA, 6 months after starting treatment, and then every 6 to 12 months thereafter, and as clinically indicated. Consider interruption of TECFIDERA in patients with lymphocyte counts less than $0.5 \times 10^9/L$ persisting for more than six months. Given the potential for delayed recovery of lymphocyte counts, continue to obtain lymphocyte counts until their recovery if TECFIDERA is discontinued or interrupted due to lymphopenia. Consider withholding treatment from patients with serious infections until resolution. Decisions about whether or not to restart TECFIDERA should be individualized based on clinical circumstances.

5.4 Liver Injury

Clinically significant cases of liver injury have been reported in patients treated with TECFIDERA in the postmarketing setting. The onset has ranged from a few days to several months after initiation of treatment with TECFIDERA. Signs and symptoms of liver injury, including elevation of serum aminotransferases to greater than 5-fold the upper limit of normal and elevation of total bilirubin to greater than 2-fold the upper limit of normal have been observed. These abnormalities resolved upon treatment discontinuation. Some cases required hospitalization. None of the reported cases resulted in liver failure, liver transplant, or death. However, the combination of new serum aminotransferase elevations with increased levels of bilirubin caused by drug-induced hepatocellular injury is an important predictor of serious liver injury that may lead to acute liver failure, liver transplant, or death in some patients.

Elevations of hepatic transaminases (most no greater than 3 times the upper limit of normal) were observed during controlled trials [see *Adverse Reactions (6.1)*].

Obtain serum aminotransferase, alkaline phosphatase (ALP), and total bilirubin levels prior to treatment with TECFIDERA and during treatment, as clinically indicated. Discontinue TECFIDERA if clinically significant liver injury induced by TECFIDERA is suspected.

5.5 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)*].
- Liver Injury [see *Warnings and Precautions (5.4)*].
- Flushing [see *Warnings and Precautions (5.5)*].

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 $\geq 10\%$ and $\geq 2\%$ 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 $\geq 2\%$ 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
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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) during controlled trials. 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.

6.2 Post Marketing Experience

The following adverse reaction has been identified during post approval use of TECFIDERA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Liver function abnormalities (elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN) have been reported following TECFIDERA administration in post marketing experience [See *Warnings and Precautions (5.4)*].

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, embryoletality 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.

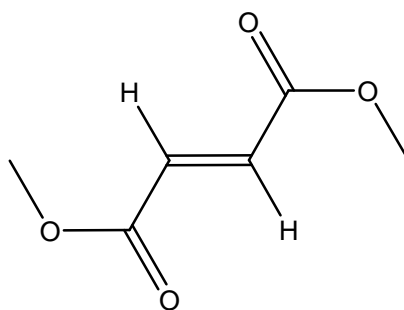
10 OVERDOSE

Cases of overdose with TECFIDERA have been reported. The symptoms described in these cases were consistent with the known adverse event profile of TECFIDERA.

There are no known therapeutic interventions to enhance elimination of TECFIDERA nor is there a known antidote. In the event of overdose, initiate symptomatic supportive treatment as clinically indicated.

11 DESCRIPTION

TECFIDERA contains dimethyl fumarate which is also known by its chemical name, dimethyl (E) butenedioate, (C₆H₈O₄). 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 C_{max} 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.

Oral Contraceptives

The coadministration of dimethyl fumarate with a combined oral contraceptive (norelgestromin and ethinyl estradiol) did not elicit any relevant effects in oral contraceptives exposure. No interaction studies have been performed with oral contraceptives containing other progestogens.

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/m²) 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 embryoletality at the highest dose tested. The highest dose not associated with adverse effects (100 mg/kg/day) is twice the RHD on a mg/m² 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.

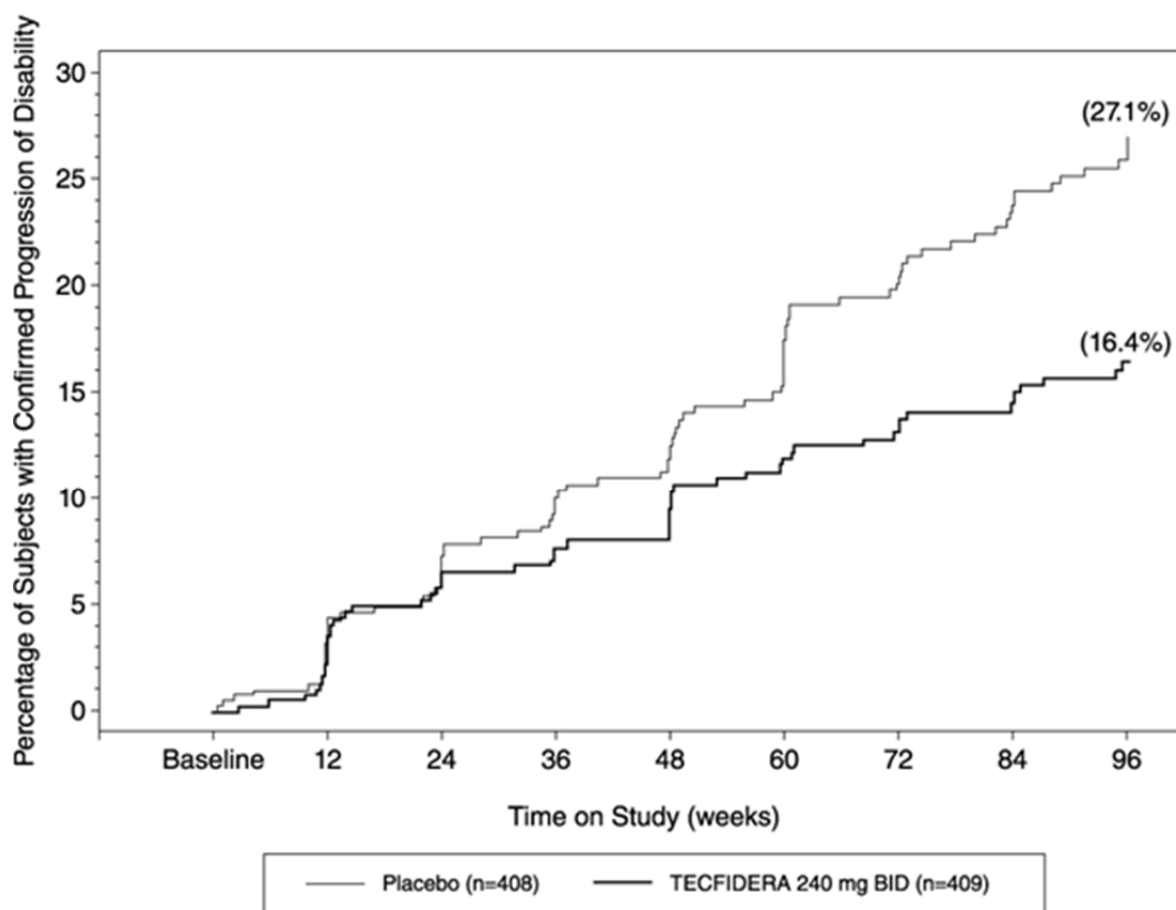
TECFIDERA had a statistically significant effect on all of the endpoints described above and the 240 mg three times daily dose showed no additional benefit over the TECFIDERA 240 mg twice daily dose. The results for this study (240 mg twice a day vs. placebo) are shown in [Table 2](#) and [Figure 1](#).

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%	

	TECFIDERA 240 mg BID	Placebo	P-value
Number of Gd+ lesions at 2 years Mean (median)	0.1 (0)	1.8 (0)	
Percentage of subjects with			
0 lesions	93%	62%	
1 lesion	5%	10%	
2 lesions	<1%	8%	
3 to 4 lesions	0	9%	
5 or more lesions	<1%	11%	
Relative odds reduction (percentage)	90%		<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 \geq 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%	

	TECFIDERA 240 mg BID	Placebo	P-value
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%		
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.

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 patients 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)*].

Liver Injury

Inform patients that TECFIDERA may cause liver injury. Instruct patients treated with TECFIDERA to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. A blood test should be obtained before patients start therapy and during treatment, as clinically indicated [*see Warnings and Precautions (5.4)*].

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)*].

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Cambridge, MA 02142

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