ART & SCIENCE OF MS

Key Topics in MS Management

Query: Should we spell out "Multiple Sclerosis (MS)"? It is not spelled out in Avonex or Corporate but probably should have been. These pages were added at the last minute.

Biogen

BIOGEN

Biogen

Tecfidera
(dimethyl fumarate) delayed-release capsules 240 mg

plegridy
(peginterferon beta-1a)

EVERY 4 WEEKS 300mg IV
TYSABRI
(natalizumab)

ONCE-A-WEEK
AVONEX
(interferon beta-1a)
IM INJECTION

INDICATION AND

TECFIDERA IMPORTANT SAFETY INFORMATION

Indication

Initial cap: Tecfidera

- TECFIDERA® (dimethyl fumarate) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

Important Safety Information

- TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Patients experiencing signs and symptoms of anaphylaxis and angioedema (which have included difficulty breathing, urticaria, and swelling of the throat and tongue) should discontinue TECFIDERA and seek immediate medical care.
- A fatal case of progressive multifocal leukoencephalopathy (PML) occurred in a patient who received 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. The 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. At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation.
- TECFIDERA may decrease lymphocyte counts; in clinical trials there was a mean decrease of ~30% in lymphocyte counts during the first year which then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but not to baseline. Six percent of TECFIDERA patients and <1% of placebo patients had lymphocyte counts $<0.5 \times 10^9$/L. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.
- There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8 \times 10^9$/L or $<0.5 \times 10^9$/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). 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 $<0.5 \times 10^9$/L with continued therapy. A complete blood count including lymphocyte count should be obtained before initiating treatment, after 6 months, every 6 to 12 months thereafter and as clinically indicated. Consider treatment interruption if lymphocyte counts $<0.5 \times 10^9$/L persist for more than six months and follow lymphocyte counts until lymphopenia is resolved. Consider withholding treatment in patients with serious infections until resolved. Decisions about whether or not to restart TECFIDERA should be based on clinical circumstances.
- TECFIDERA may cause flushing (e.g. warmth, redness, itching, and/or burning sensation). 40% of patients taking TECFIDERA reported flushing which was mostly mild to moderate in severity. Three percent of patients discontinued TECFIDERA for flushing and <1% had serious flushing events that led to hospitalization. Taking TECFIDERA with food may reduce flushing. Alternatively, administration of non-enteric coated aspirin prior to dosing may reduce the incidence or severity of flushing.
- TECFIDERA may cause gastrointestinal (GI) events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). Four percent of TECFIDERA patients and <1% placebo patients discontinued due to GI events. The incidence of serious GI events was 1%. The most common adverse reactions associated with TECFIDERA versus placebo are flushing (40% vs 6%) and GI events: abdominal pain (18% vs 10%), diarrhea (14% vs 11%), nausea (12% vs 9%).
- Elevations in hepatic transaminases have been reported. A transient increase in mean eosinophil counts was seen during the first two months. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage patients who become pregnant while taking TECFIDERA to enroll in the TECFIDERA pregnancy registry by calling 1-866-810-1462 or visiting www.TECFIDERApregnancyregistry.com.

Add pls see line:
Please see full Prescribing Information for TECFIDERA for additional important safety information.

EXIT CONTINUE

#1 PRESCRIBED ORAL THERAPY FOR RELAPSING MS IN THE US SINCE SEPTEMBER 2013*

UNITED STATES

MULTIPLE SCLEROSIS

Spell out?

ok

*Based on the number of prescriptions from IMS NPA™ Weekly Data (September 27, 2013 to December 31, 2014).

REF

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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, Liver Injury (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 daily for 7 days (2.1)
- Maintenance dose after 7 days: 240 mg twice daily (2.1)
- Swallow TECFIDERA capsules whole and intact. Do not crush, chew, or sprinkle the capsule contents on food. (2.2)
- Take TECFIDERA with or without food. (2.2)

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 assess TECFIDERA if these occur. (5.1)
- Progressive multifocal leukoencephalopathy (PML): Withhold TECFIDERA if the first sign or symptom suggestive of PML. (5.2)
- Lymphopenia: Consider withholding TECFIDERA treatment in patients with a lymphocyte count below 0.5 x 10^9/L for more than 6 months. Consider discontinuing TECFIDERA if lymphopenia persists for 6 to 24 months. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10% and ≥2% placebo) were flushing, abdominal pain, diarrhea, and nausea. (6)

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: 4/2015

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. When dosing for 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 tolerability 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 (5.5)]*.

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 and white body; printed with "BIIB" and "32 120 mg" in black ink on the body. The 240 mg capsules have a green cap and a green body, printed with "BIIB" and "32 240 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 has usually leads to death or severe disability. During the clinical trial, the patient experienced prolonged lymphopenia (lymphocyte counts predominantly below 0.5 x 10^9/L for more than 4 years). The patient's JCV antibody status was positive. 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 <0.8x10^9/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 herpes meningoencephalitis requiring hospitalization and discontinuation of treatment with lymphocyte counts <0.5x10^9/L for 15 months *[see Warnings and Precautions (5.2)]*. In controlled clinical trials, 2% of patients experienced lymphocyte counts <0.5 x 10^9/L for at least six months. In these patients, the majority of lymphocyte counts remained >0.5 x10^9/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 patient-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 Reaction in Study 1 and 2 reported for TECFIDERA 240 mg BID at ≥ 2% higher incidence than placebo

	TECFIDERA (%)	Placebo (%)
Flushing	40	6
Abdominal pain	18	10
Diarrhea	14	11
Nausea	12	9
Vomiting	9	5
Flushed	5	2
Rash	5	2
Albumin urine present	6	4
Erythema	3	1
Dyspepsia	3	2
Alanine aminotransferase increased	4	2
Lymphopenia	3	<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 2% of placebo patients discontinued because of 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 increase in bilirubin > 2 times the ULN. Discontinuation 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 have followed for exposure to TECFIDERA for a maximum of 4 years and 1650 patients have approximately 3 years of exposure. 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) of dimethyl fumarate (DMF), the active metabolite of dimethyl 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 rats and human 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 2 x 240 mg) following administration of TECFIDERA in healthy subjects. The mean C_{max} and AUC of MMF were 1.87 mg/L and AUC was 8.23 mg/L·hr 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 22% 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 are excreted 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

or glutamyser 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 nonphamacic renal (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 vivo* 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) for 480 mg/day on a body surface area basis.

In female rats, oral administration of DMF (20, 100, and 250 mg/kg/day) prior to and during mating and continuation 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/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 experienced at least 1 relapse in 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.

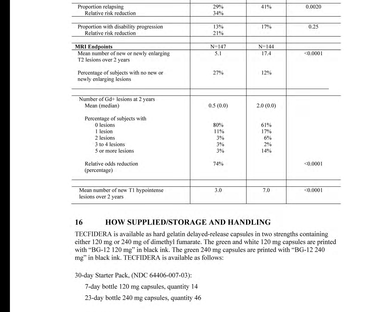
Missing a paragraph: Patients randomized to receive TECFIDERA 240 mg twice a day (N=410), TECFIDERA 240 mg three times a day (N=408), or placebo (N=363) for up to 2 years. The median age was 39 years, the median time since diagnosis was 5 years, and median EDSS score at baseline was 2.5. The median time on study drug for all treatment arms was 96 weeks. The percentage of patients who completed 96 weeks on study drug treatment was 80% 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)	27%	46%	<0.0001
Relative risk reduction	49%		
Annualized relapse rate	0.172	0.364	<0.0001
Relative reduction	53%		
Proportion with disability progression	16%	27%	0.0050
Relative risk reduction	38%		
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)	0.1 (0)	1.8 (0)	
Percentage of subjects with			
0 lesions	95%	62%	
1 lesion	5%	18%	
2 lesions	<3%	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 >= 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.

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)]*.

41347-06

Manufactured by:
Biogen Inc.
Cambridge, MA 02142

TECFIDERA is a registered trademark of Biogen.

© Biogen 2013 - 2015

Patient Information
TECFIDERA® (tek' f 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 the 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.

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 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 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 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: 4/2015

THE PROPOSED MOA FOR TECFIERA

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

PROPOSED MOA

In multiple sclerosis (MS), inflammation and neurologic oxidative stress can create a cyclical process that may lead to progressive damage[1]

- The mechanism by which TECFIDERA exerts its therapeutic effect in MS is unknown[2]
- TECFIDERA and the metabolite monomethyl fumarate activate the nuclear factor (erythroid-derived 2)-like (Nrf2) pathway, which is involved in the cellular response to oxidative stress[2]
- Nrf2 activity is upregulated in response to oxidative stress in MS[3]

TECFIDERA offers a different approach to the treatment of relapsing MS.[4]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

THE PROPOSED MOA FOR TECFIERA

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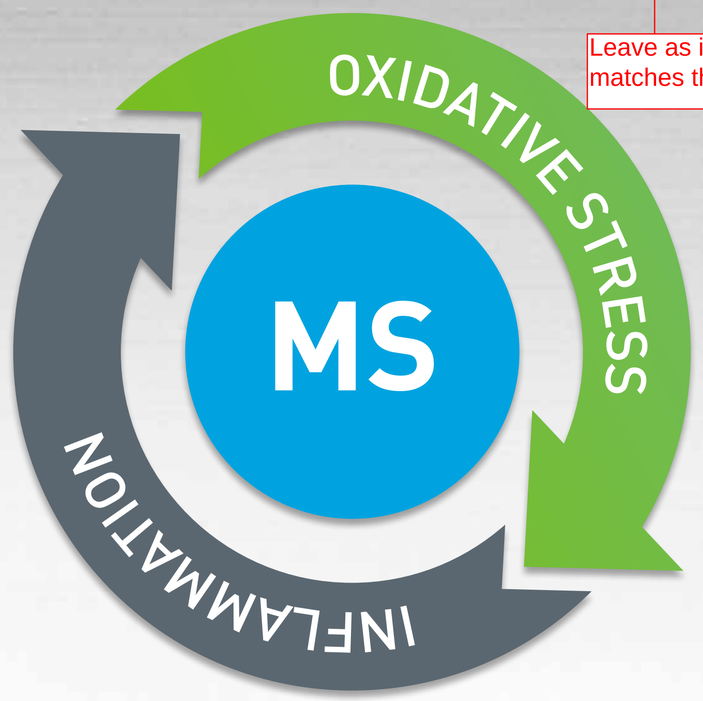
STET

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg



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References

1. Innamorato NG, Rojo AI, García-Yagüe AJ, Yamamoto M, de Ceballos ML, Cuadrado A. The transcription factor Nrf2 is a therapeutic target against brain inflammation. *J Immunol.* 2008;181(1):680-689.
2. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
3. van Horssen J, Witte ME, Schreibelt G, de Vries HE. Radical changes in multiple sclerosis pathogenesis. *Biochim Biophys Acta.* 2011;1812(2):141-150.
4. TECFIDERA website. The potential of Nrf2. http://www.tecfiderahcp.com/clinical-overview/moa.html. Accessed April 15, 2015.

INDICATION AND

TECFIDERA IMPORTANT SAFETY INFORMATION

Indication

Initial cap: Tecfidera

- TECFIDERA® (dimethyl fumarate) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

Important Safety Information

- TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Patients experiencing signs and symptoms of anaphylaxis and angioedema (which have included difficulty breathing, urticaria, and swelling of the throat and tongue) should discontinue TECFIDERA and seek immediate medical care.
- A fatal case of progressive multifocal leukoencephalopathy (PML) occurred in a patient who received 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. The 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. At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation.
- TECFIDERA may decrease lymphocyte counts; in clinical trials there was a mean decrease of ~30% in lymphocyte counts during the first year which then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but not to baseline. Six percent of TECFIDERA patients and <1% of placebo patients had lymphocyte counts $<0.5 \times 10^9$/L. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.
- There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8 \times 10^9$/L or $<0.5 \times 10^9$/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). 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 $<0.5 \times 10^9$/L with continued therapy. A complete blood count including lymphocyte count should be obtained before initiating treatment, after 6 months, every 6 to 12 months thereafter and as clinically indicated. Consider treatment interruption if lymphocyte counts $<0.5 \times 10^9$/L persist for more than six months and follow lymphocyte counts until lymphopenia is resolved. Consider withholding treatment in patients with serious infections until resolved. Decisions about whether or not to restart TECFIDERA should be based on clinical circumstances.
- TECFIDERA may cause flushing (e.g. warmth, redness, itching, and/or burning sensation). 40% of patients taking TECFIDERA reported flushing which was mostly mild to moderate in severity. Three percent of patients discontinued TECFIDERA for flushing and <1% had serious flushing events that led to hospitalization. Taking TECFIDERA with food may reduce flushing. Alternatively, administration of non-enteric coated aspirin prior to dosing may reduce the incidence or severity of flushing.
- TECFIDERA may cause gastrointestinal (GI) events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). Four percent of TECFIDERA patients and <1% placebo patients discontinued due to GI events. The incidence of serious GI events was 1%. The most common adverse reactions associated with TECFIDERA versus placebo are flushing (40% vs 6%) and GI events: abdominal pain (18% vs 10%), diarrhea (14% vs 11%), nausea (12% vs 9%).
- Elevations in hepatic transaminases have been reported. A transient increase in mean eosinophil counts was seen during the first two months. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage patients who become pregnant while taking TECFIDERA to enroll in the TECFIDERA pregnancy registry by calling 1-866-810-1462 or visiting www.TECFIDERApregnancyregistry.com.

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

TECFIDERA WAS EVALUATED IN TWO PHASE 3 STUDIES

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Two, 2-year, randomized, double-blind, placebo-controlled trials[1]

DEFINE* Trial[2]

Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (MS).[2]

CONFIRM† Trial[3]

Comparator and an Oral Fumarate in Relapsing-Remitting MS.[3]

Efficacy and safety were demonstrated in 2 controlled clinical trials.[1]

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References

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
2. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis [published correction appears in *N Engl J Med*. 2012;367(24):2362]. *N Engl J Med*. 2012;367(12):1098-1107.
3. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis [published correction appears in *N Engl J Med*. 2012;367(17):1673]. *N Engl J Med*. 2012;367(12):1087-1097.

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Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

THE DEFINE* TRIAL DESIGN

per IVA: relapsing-remitting multiple sclerosis (RRMS)

A 2-year, randomized, double-blind, placebo-controlled study in 1234 patients with relapsing multiple sclerosis (RMS)[1]

page 17 has 1,2. Should match.

delete per pg 34?

No, let's leave it in to match the IVA, I added it on page 34. Thanks!

RANDOMIZATION†

- **TECFIDERA PO 240 mg** n=410 — One 120-mg capsule twice a day for the first 7 days, followed by an increase to one 240-mg capsule twice a day
  ~~(dimethyl fumarate)~~
- **Placebo** n=408

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Evaluations[1]	Endpoints[1]	Key Exclusion Criteria[1]	Key Inclusion Criteria[1]
Neurological evaluations Performed at baseline, every 3 months, and at time of suspected relapse	**Primary** Proportion of patients relapsed Delete Not in IVA	Interferon-alpha, interferon-beta, or glatiramer acetate within 3 months of randomization	Experienced at least 1 relapse over the year preceding the trial **OR** Had a brain MRI scan demonstrating at least 1 Gd+ lesion within 6 weeks of randomization **AND** EDSS score ranging from 0 to 5
MRI evaluations Performed in 44% of patients at baseline, Month 6, and Years 1 and 2	**Additional** Annualized relapse rate Time to confirmed disability progression Number of new or newly enlarging T2 hyperintense lesions Number of Gd+ lesions Number of new T1 hyperintense lesions	An infusion DMT within 6 months of randomization Add per IVA: Primary progressive MS or secondary progressive MS Any major disease that would preclude participation in a clinical trial	

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; MRI=magnetic resonance imaging.

*Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (MS).[2]
†Study also randomized patients (n=416) to a 240-mg TID arm. TID dosing resulted in no additional benefit over 240 mg BID.[1]

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THE DEFINE* TRIAL DESIGN

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Evaluations[1]	Endpoints[1]	Key Exclusion Criteria[1]	Key Inclusion Criteria[1]
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MRI evaluations	**Additional**	An infusion DMT within	

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DEFINE* TRIAL: PATIENT DEMOGRAPHICS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

EFFICACY
Efficacy Trials
DEFINE Patient Demographics
DEFINE Proportion of Patients Relapsed
DEFINE Annual Relapse Rate
DEFINE Disability Progression
DEFINE MRI Activity
DEFINE T2 and T1 Lesions
CONFIRM Patient Demographics
CONFIRM Results
SD
REF
PI
ISI

A 2-year, randomized, double-blind, placebo-controlled study in 1234 patients with relapsing multiple sclerosis (RMS)[1,2]

59% Treatment-naïve[2]	**41%** Previously approved MS medications[2]
4 Median years since diagnosis[1]	**2** Median EDSS baseline scores[1]

EDSS=Expanded Disability Status Scale.
*Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS.[2]

TECFIDERA was evaluated in both treatment-naïve and treatment-experienced patients.[2]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

DEFINE* TRIAL: PATIENT DEMOGRAPHICS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

per IVA: relapsing-remitting multiple sclerosis (RRMS)

Change

A 2-year, randomized, double-blind, placebo-controlled study in 1234 patients with relapsing multiple sclerosis (RMS)[1,2]

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DEFINE* TRIAL: PATIENT DEMOGRAPHICS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

A 2-year, randomized, double-blind, placebo-controlled study in 1234 patients with relapsing multiple sclerosis (RMS)[1,2]

59% Treatment-naïve[2]	**41%** Previously approved MS medications[2]
4	**2**

treatment-experienced patients.[2]

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References

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
2. Biogen, Data on file.
3. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis [published correction appears in *N Engl J Med*. 2012;367(24):2362]. *N Engl J Med*. 2012;367(12):1098-1107.

A DEFINITIVE REDUCTION IN RELAPSES IN THE 2-YEAR DEFINE* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

EFFICACY

- Efficacy Trials
- DEFINE Patient Demographics
- DEFINE Proportion of Patients Relapsed
- DEFINE Annual Relapse Rate
- DEFINE Disability Progression
- DEFINE MRI Activity
- DEFINE T2 and T1 Lesions
- CONFIRM Patient Demographics
- CONFIRM Results

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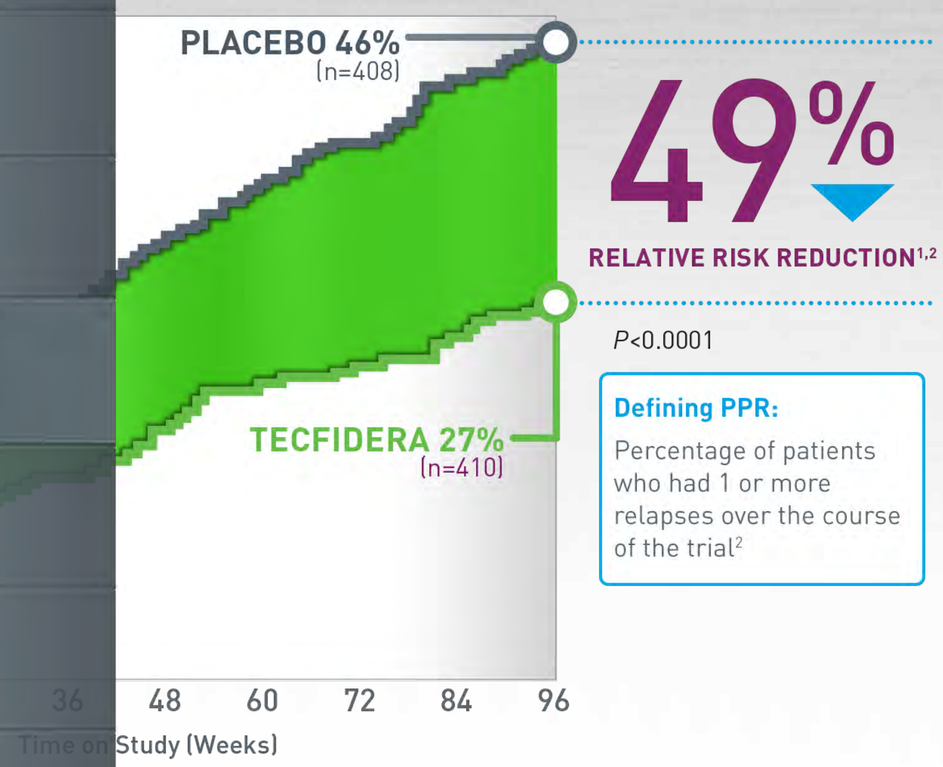
PROPORTION OF PATIENTS RELAPSED (PPR)†



Defining PPR:
Percentage of patients who had 1 or more relapses over the course of the trial[2]

- TECFIDERA patients were about *half as likely to have a relapse* as placebo patients—which means fewer of *your* members may have a relapse over 2 years[1]

*Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.[2]
†Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.[2]

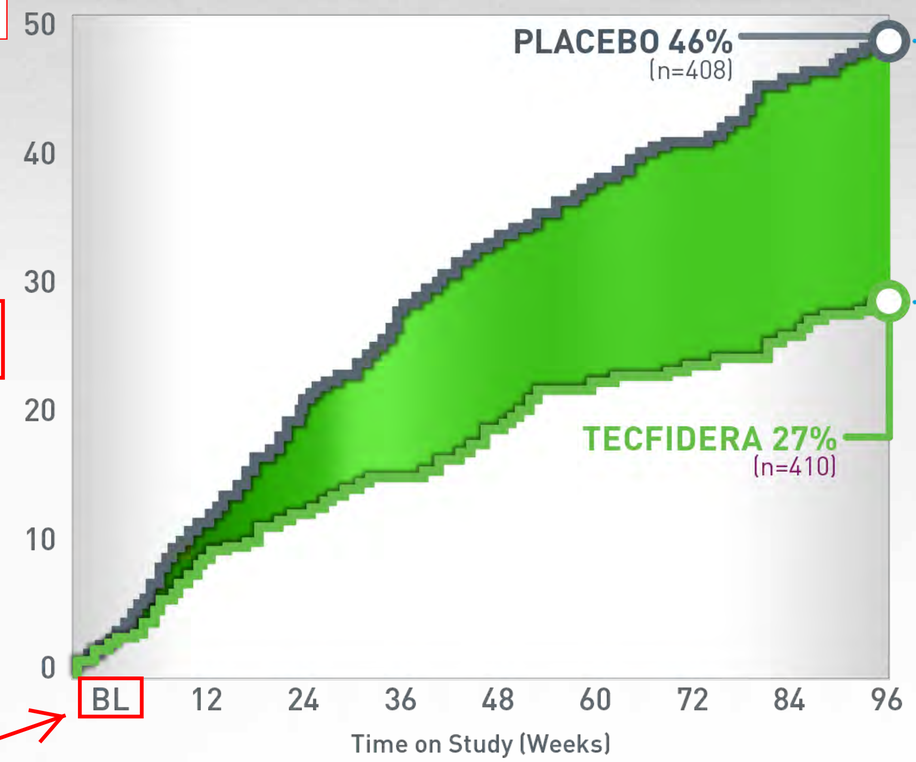
73% of TECFIDERA patients were free of relapse at 96 weeks.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

A DEFINITIVE REDUCTION IN RELAPSES IN THE 2-YEAR DEFINE* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

PROPORTION OF PATIENTS RELAPSED (PPR)†



49% RELATIVE RISK REDUCTION[1,2]

$P<0.0001$

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Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

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PPR

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Global: bold/ital

IVA says "patients"

Leave as is

SD
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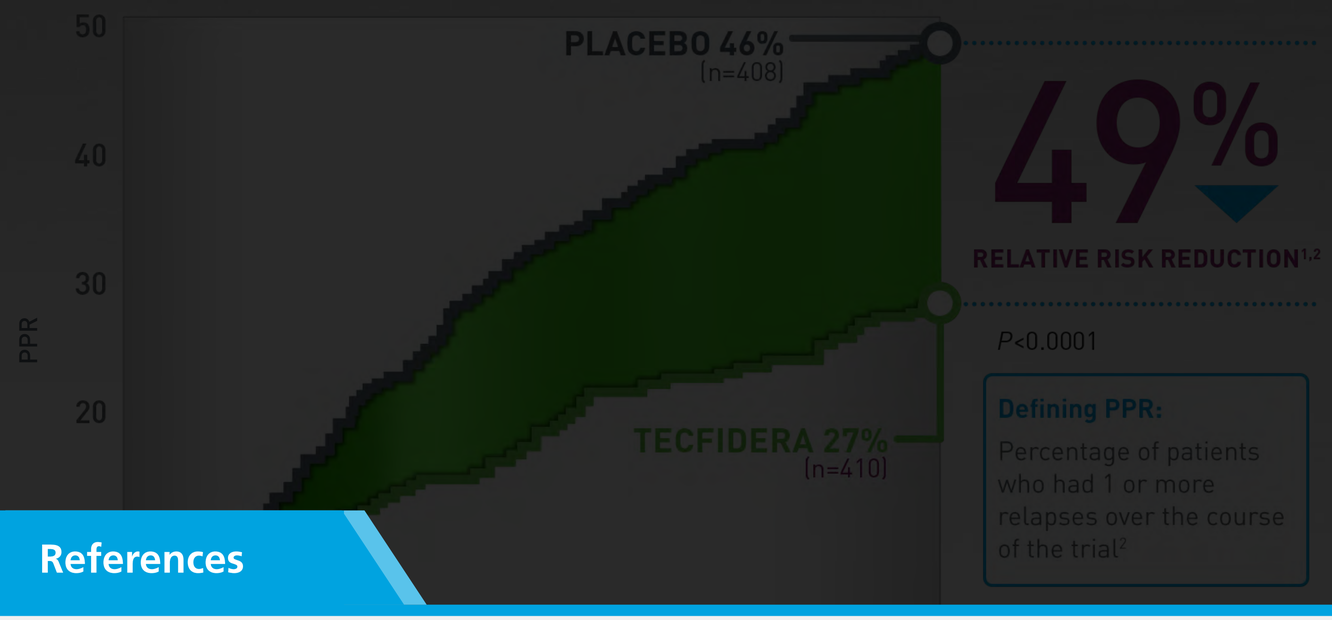
A DEFINITIVE REDUCTION IN RELAPSES IN THE 2-YEAR DEFINE* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

PROPORTION OF PATIENTS RELAPSED (PPR)†



- TECFIDERA patients were about half as likely to have a relapse as placebo patients—which means fewer of *your* members may have a relapse over 2 years[1]

References

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
2. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis [published correction appears in *N Engl J Med*. 2012;367(24):2362]. *N Engl J Med*. 2012;367(12):1098-1107.

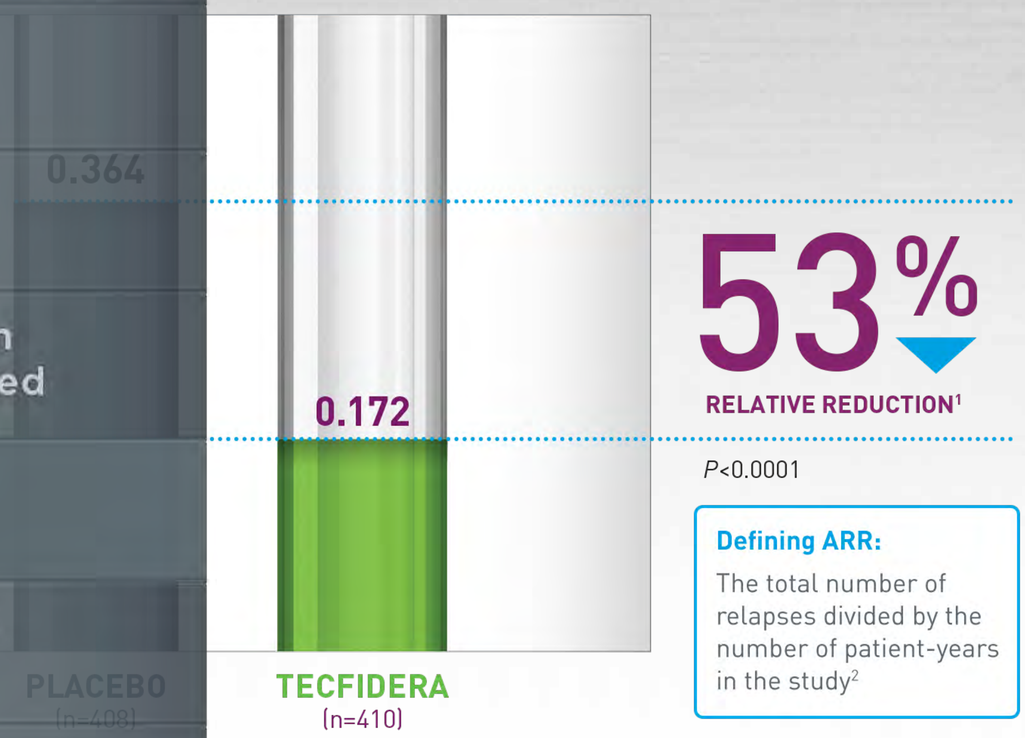
73% of TECFIDERA patients were free of relapse at 96 weeks.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

A DEFINITIVE REDUCTION IN ANNUALIZED RELAPSE RATE IN THE 2-YEAR DEFINE* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

ANNUALIZED RELAPSE RATE (ARR)†



53% RELATIVE REDUCTION[1]

P<0.0001

Defining ARR:
The total number of relapses divided by the number of patient-years in the study[2]

- TECFIDERA patients had about half as many relapses per year as placebo patients—which may mean fewer relapses for *your* members[1]

*Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.[2]
†Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.[2]

TECFIDERA was associated with an 83% annualized relapse-free rate.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

A DEFINITIVE REDUCTION IN ANNUALIZED RELAPSE RATE IN THE 2-YEAR DEFINE* TRIAL

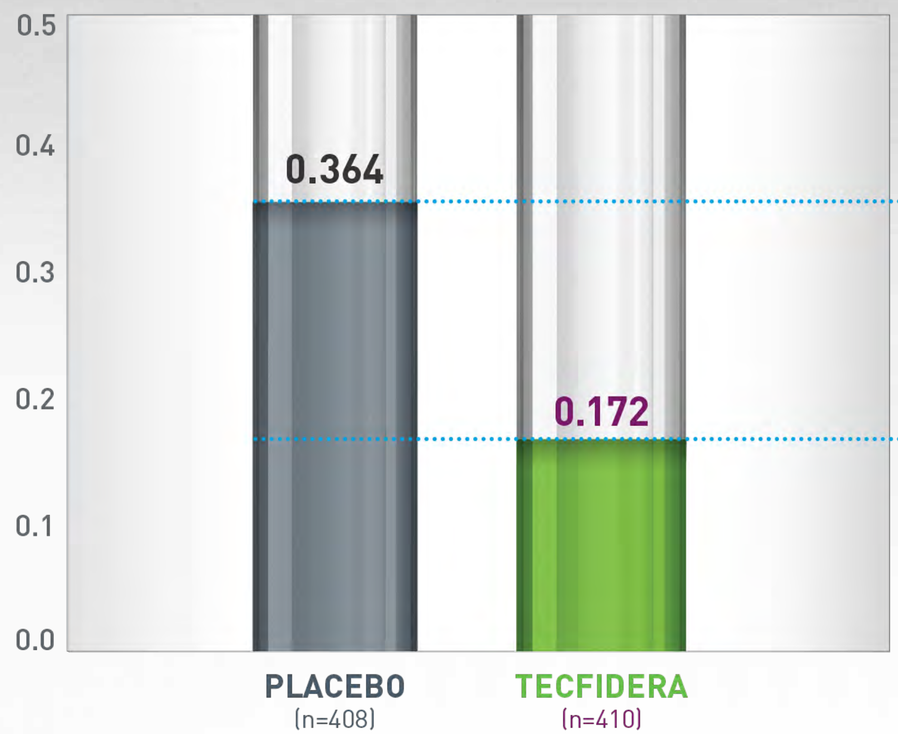
Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Yes: Adjusted Annualized Relapse Rate

This is spelled out in IVA but is called out above. Ok as is?

Add: Adjusted

ANNUALIZED RELAPSE RATE (ARR)†



53% RELATIVE REDUCTION[1]

P<0.0001

Defining ARR:
The total number of relapses divided by the number of patient-years in the study[2]

Ital

- TECFIDERA patients had about half as many relapses per year as placebo patients—which may mean fewer relapses for *your* members[1]

IVA says: your patients over 2 years

Should this be purple to match pg 20?

No all text should be black

Leave as is

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A DEFINITIVE REDUCTION IN ANNUALIZED RELAPSE RATE IN THE 2-YEAR DEFINE* TRIAL

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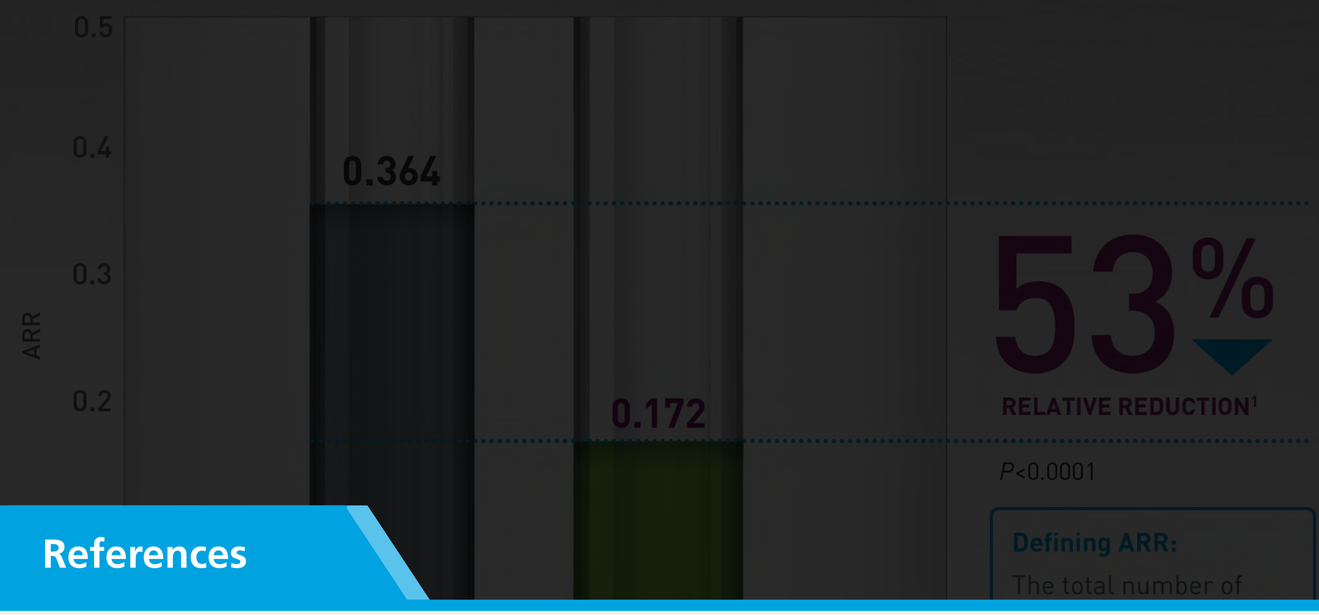
ANNUALIZED RELAPSE RATE (ARR)†



Defining ARR:
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TECFIDERA was associated with an 83% annualized relapse-free rate.[1]

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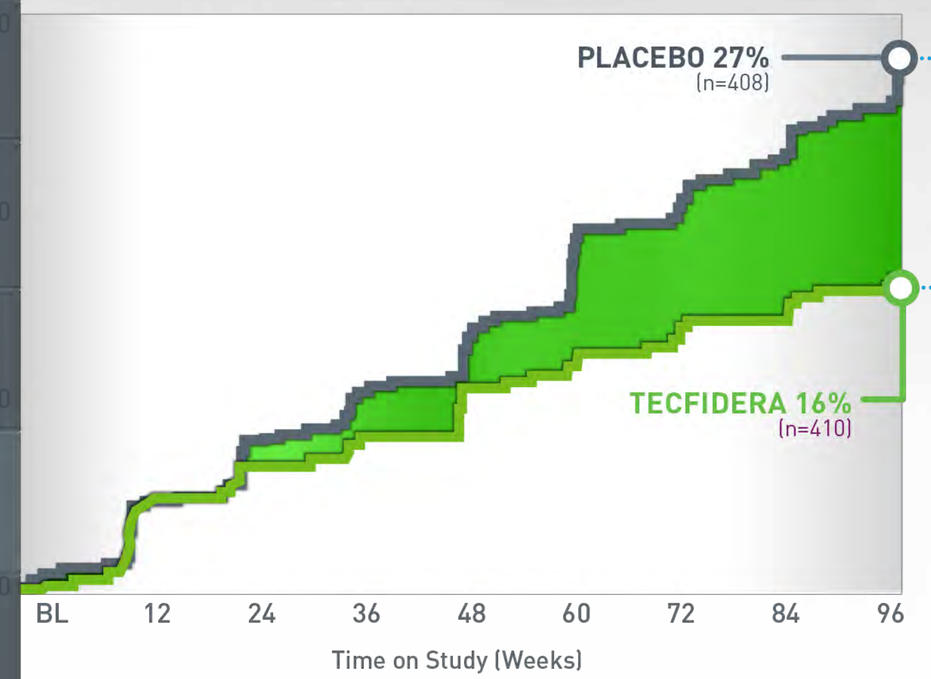
DISABILITY PROGRESSION SIGNIFICANTLY DELAYED IN THE 2-YEAR DEFINE* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

This means that more of *your* members may be able to avoid disability progression for longer periods of time

TIME TO PROGRESSION OF DISABILITY



38% RELATIVE RISK REDUCTION[1]

P=0.0050

Defining Disability Progression:
At least a 1-point increase from baseline EDSS of ≥1.0, OR at least a 1.5-point increase for patients with baseline EDSS of 0 sustained for 12 weeks[1]

EDSS=Expanded Disability Status Scale.
*Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.[2]

84% of TECFIDERA patients experienced no disability progression over the 2-year study period.[1]

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DISABILITY PROGRESSION SIGNIFICANTLY DELAYED IN THE 2-YEAR DEFINE* TRIAL

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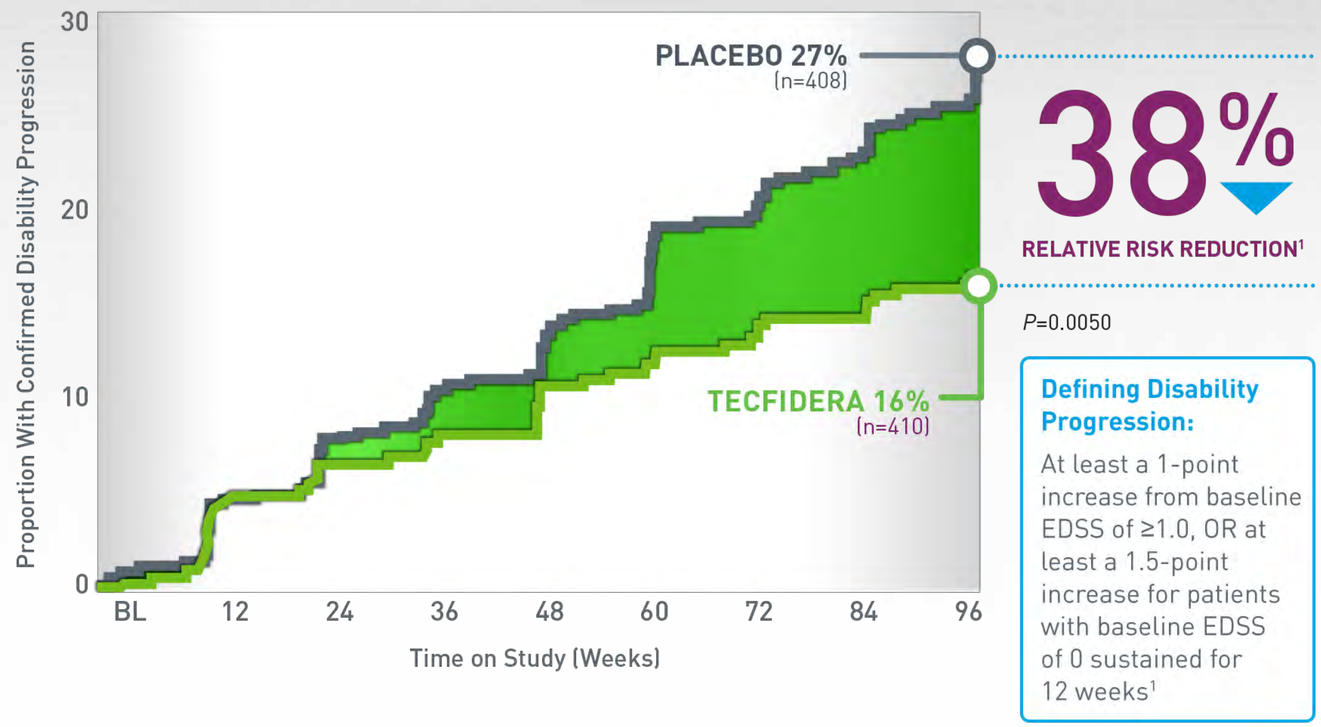
Should this be green to match style on pg 20

Fine as is

TIME TO PROGRESSION OF DISABILITY



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DISABILITY PROGRESSION SIGNIFICANTLY DELAYED IN THE 2-YEAR DEFINE* TRIAL

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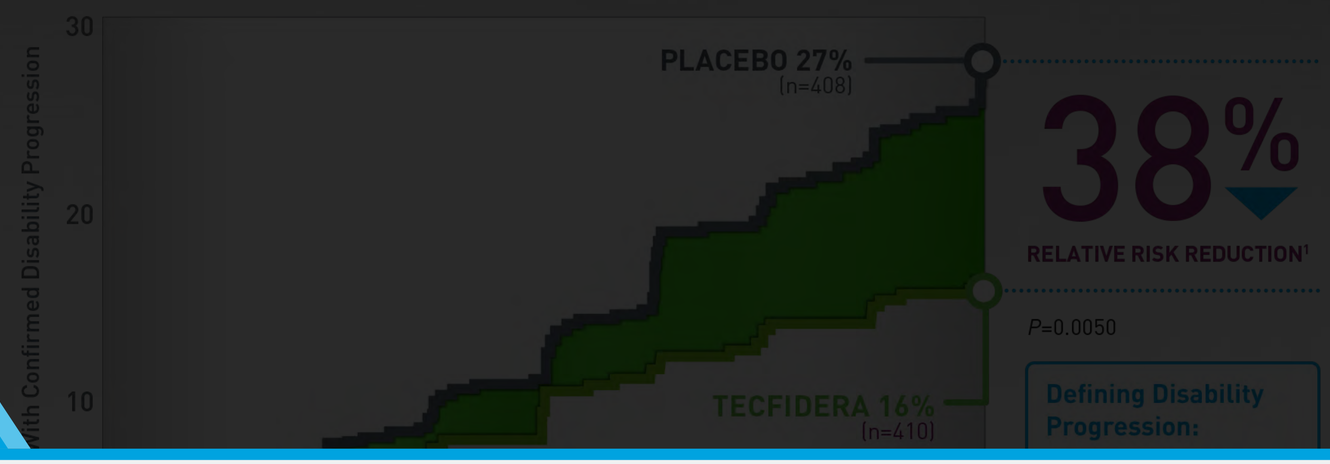

References

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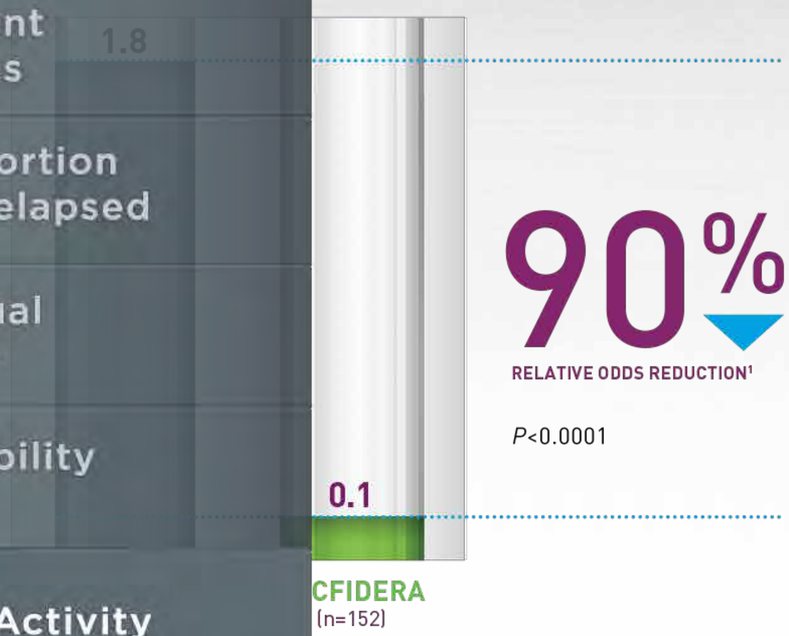
MAGNETIC RESONANCE IMAGING ACTIVITY SIGNIFICANTLY REDUCED IN THE 2-YEAR DEFINE* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Gadolinium-enhancing (Gd+) lesions were significantly reduced vs placebo at 2 years—which may mean less magnetic resonance imaging (MRI) activity for your members[1]

Number of Gd+ Lesions at 2 Years



Percentage of Patients With Gd+ Lesions at 2 Years[1]

	TECFIDERA (n=152)	PLACEBO (n=165)
0 lesions	93%	62%
1 lesion	5%	10%
2 lesions	<1%	8%
3 to 4 lesions	0%	9%
5 or more lesions	<1%	11%

*Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.[2]

Gd+ lesions were significantly reduced compared with placebo patients.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

MAGNETIC RESONANCE IMAGING ACTIVITY SIGNIFICANTLY REDUCED IN THE 2-YEAR DEFINE* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

"vs placebo " not in IVA

Delete

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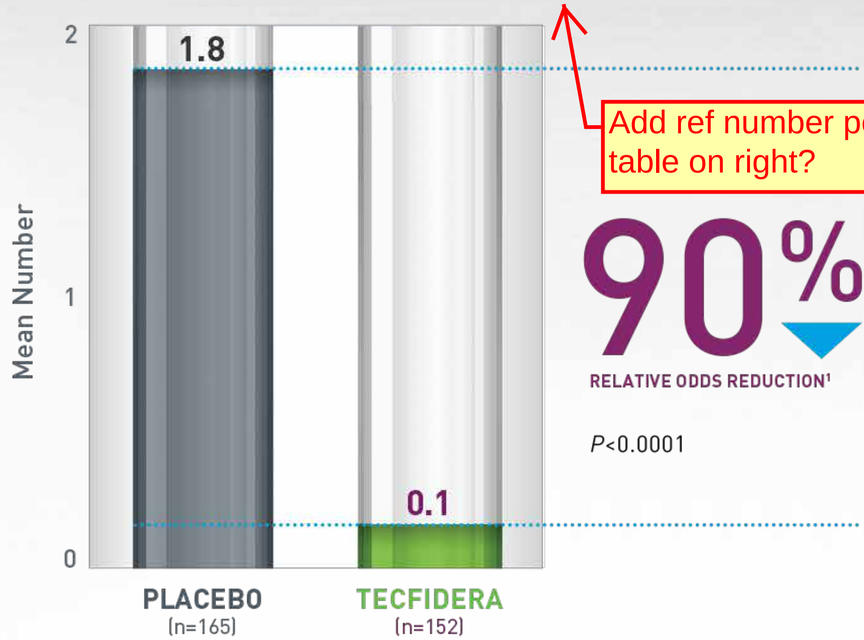
move copy per IVA?

Number of Gd+ Lesions at 2 Years



Add ref number per table on right?

90% RELATIVE ODDS REDUCTION[1]

$P<0.0001$

Percentage of Patients With Gd+ Lesions at 2 Years[1]

Yes

no

	TECFIDERA (n=152)	PLACEBO (n=165)
0 lesions	93%	62%
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Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

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MAGNETIC RESONANCE IMAGING ACTIVITY SIGNIFICANTLY REDUCED IN THE 2-YEAR DEFINE* TRIAL

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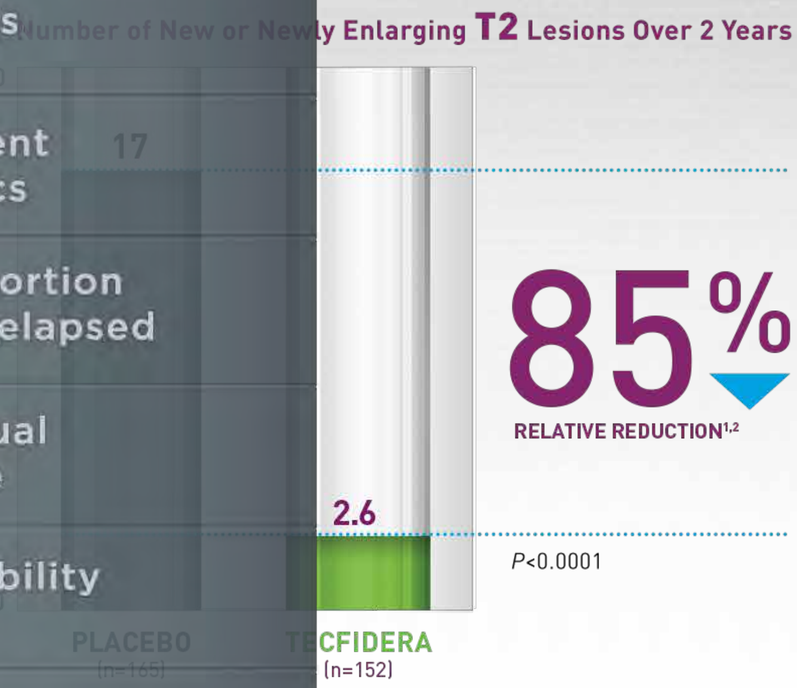
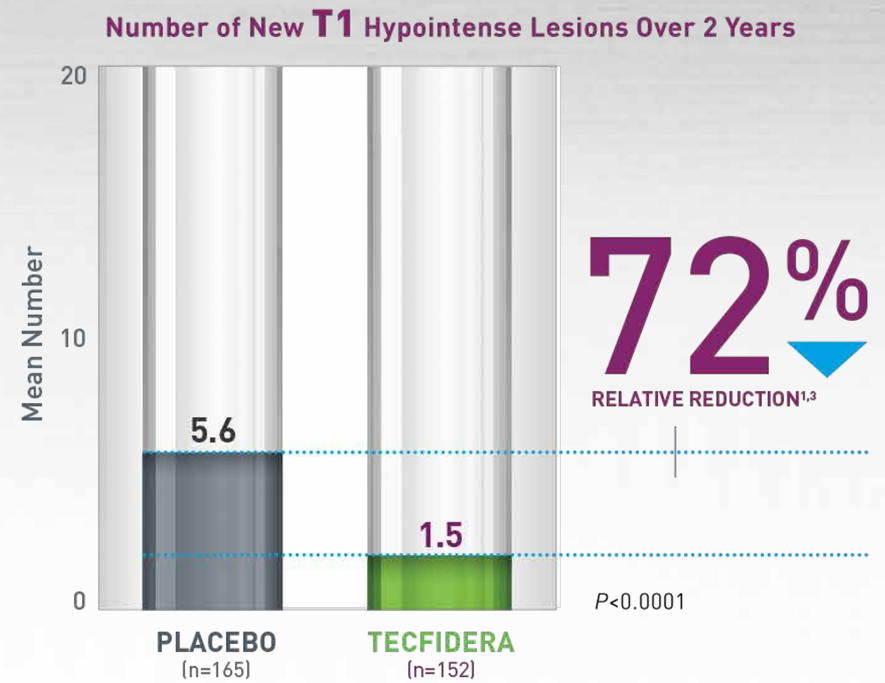
MAGNETIC RESONANCE IMAGING ACTIVITY SIGNIFICANTLY REDUCED IN THE 2-YEAR DEFINE* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

New T2 and T1 lesions were significantly reduced at 2 years—which may mean less magnetic resonance imaging (MRI) activity for your members[1,2]





Adapted from Phase 3 Trial to Evaluate the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.[2]

New or newly enlarging T2 and T1 lesions were significantly reduced compared with placebo patients.[1,2]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

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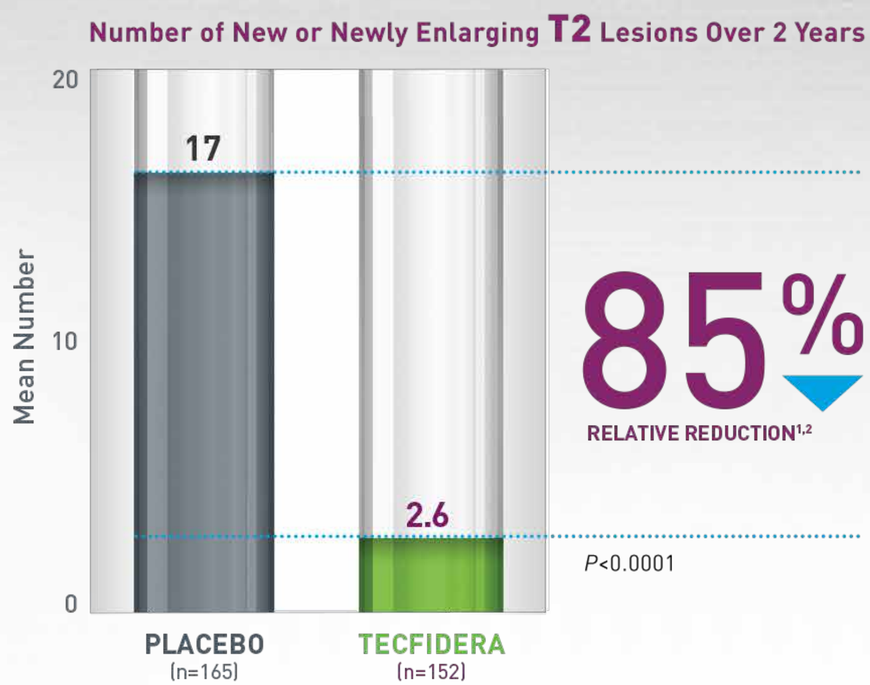

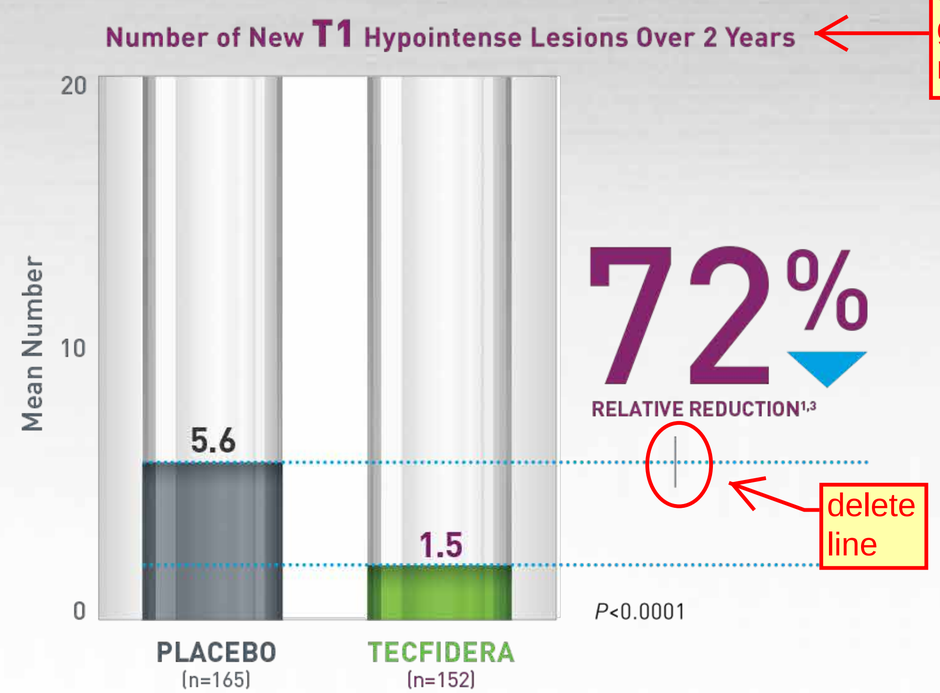

Do titles of graphs need ref numbers?

No

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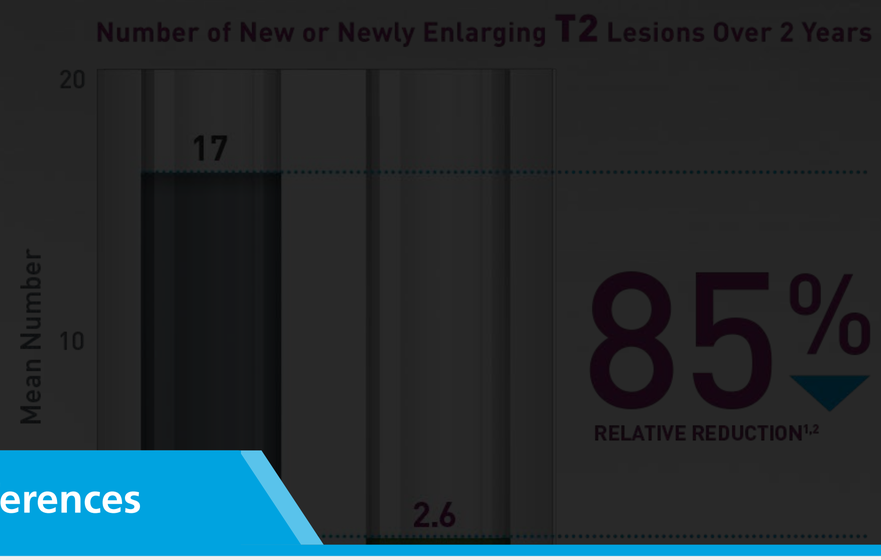

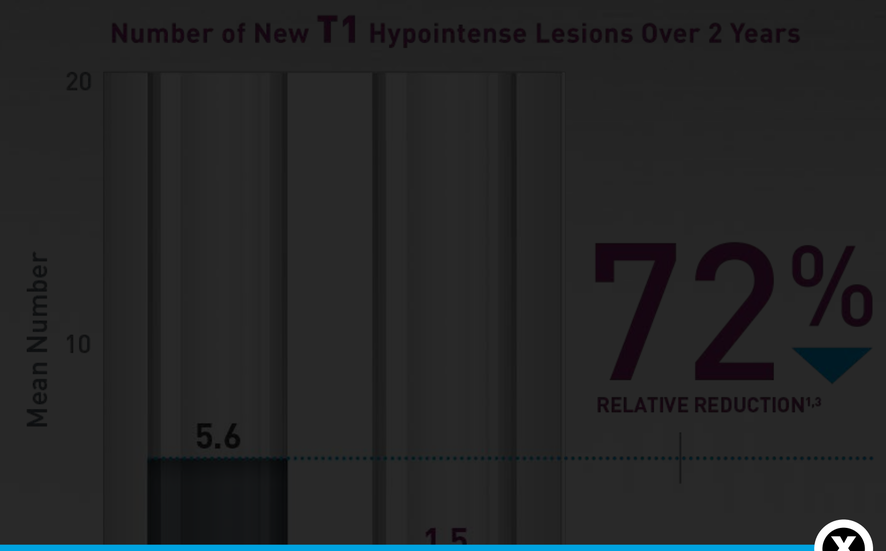

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References

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THE CONFIRM* TRIAL DESIGN

A 2-year, multicenter, randomized, double-blind, placebo-controlled study that also included an open-label comparator in 1417 patients with relapsing multiple sclerosis (RMS)[1,2]

IVA says RRMS

Replace with "relapsing-remitting multiple sclerosis (RRMS)"

RANDOMIZATION†

- **TECFIDERA PO 240 mg** n=359 — One 120-mg capsule twice a day for the first 7 days, followed by an increase to one 240-mg capsule twice a day
- (dimethly fumarate) n=363
- lowercase
- **Open-Label Comparator** n=350

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Evaluations[1]	Endpoints[1]	Key Exclusion Criteria[1]	Key Inclusion Criteria[1]
Neurological evaluations Performed at baseline, every 3 months, and at time of suspected relapse	**Primary** Annualized relapse rate not in IVA	Interferon-alpha or interferon-beta within 3 months of randomization	Experienced at least 1 relapse over the year preceding the trial **OR** Had a brain MRI scan demonstrating at least 1 Gd+ lesion within 6 weeks of randomization **AND** EDSS score ranging from 0 to 5
MRI evaluations Performed in 48% of patients at bas Month 6, and Y and 2 Remove bold	**Additional** per IVA ~~Additional~~ **time to confirmed disability progression** Number of new or newly enlarging T2 hyperintense lesions Number of Gd+ lesions Number of new T1 hypointense lesions Proportion of patients relapsed Time to confirmed disability progression	An infusion DMT within 6 months of randomization Any prior treatment with glatiramer acetate Not in IVA delete delete duplicate	

Insert: Proportion of patients relpased

Add to Key Exclusion Criteria per IVA:
Primary progressive MS or secondary progressive MS
Any major disease that would preclude participation in a clinical trial

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; MRI=magnetic resonance imaging.
*Comparator and an Oral Fumarate in Relapsing-Remitting MS.[2]
†Study also randomized patients (n=345) to a 240-mg TID arm. TID dosing resulted in no additional benefit over 240 mg BID.

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

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CONFIRM* TRIAL PATIENT DEMOGRAPHICS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

A 2-year, multicenter, randomized, double-blind, placebo-controlled study that also included an open-label comparator in 1417 patients with relapsing multiple sclerosis (RMS) who were aged 18 to 56 years[1-3]

71% Treatment-naïve[2]

29% Previously approved MS medications[2]

3 Median years since diagnosis[1]

2.5 Median EDSS baseline score[1]

EDSS=Expanded Disability Status Scale.
*Comparator and an Oral Fumarate in Relapsing-Remitting MS.[2]

TECFIDERA was evaluated in both treatment-naïve and treatment-experienced patients.[2]

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arm

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-remitting

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Doesn't match IVA. Ok as is?

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treatment-experienced patients.

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RESULTS FROM THE 2-YEAR CONFIRM* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

EFFICACY

Efficacy Trials

DEFINE Patient Demographics

DEFINE Proportion of Patients Relapsed

DEFINE Annual Relapse Rate

DEFINE Disability Progression

DEFINE MRI Activity

DEFINE T2 and T1 Lesions

CONFIRM Patient Demographics

CONFIRM Results

SD

REF

PI

ISI

Annualized relapse rate (ARR)[1†]

44% RELATIVE REDUCTION

Placebo 0.401
TECFIDERA 0.224
(P<0.0001)

TECFIDERA was associated with a 78% annualized relapse-free rate

Proportion of patients relapsed (PPR)[1†]

34% RELATIVE RISK REDUCTION

Placebo 41%
TECFIDERA 29%
(P=0.0020)

71% of TECFIDERA patients were free of relapse at 2 years

In CONFIRM, the reduction in the proportion with disability progression[‡] was not statistically significant[1]

21% RELATIVE RISK REDUCTION

Placebo 17%
TECFIDERA 13%
(P=0.25)

87% of TECFIDERA patients had no disability progression at 2 years

TECFIDERA n=359; Placebo n=363

Mean number of Gd+ lesions at 2 years[1]

74% RELATIVE ODDS REDUCTION

Placebo 2.0
TECFIDERA 0.5
(P<0.0001)

Mean number of new or newly enlarging T2 lesions over 2 years[1,2]

71% RELATIVE REDUCTION

Placebo 17.4
TECFIDERA 5.1
(P<0.0001)

Mean number of new T1 lesions over 2 years[1,2]

57% RELATIVE REDUCTION

Placebo 7.0
TECFIDERA 3.0
(P<0.0001)

TECFIDERA n=147; Placebo n=144

Gd+=gadolinium enhancing.

*Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.[2]

†Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.[2]

‡Disability progression was defined as at least a 1-point increase from baseline Expanded Disability Status Scale (EDSS) of ≥1.0 or at least a 1.5-point increase for patients baseline EDSS of 0 sustained for 12 weeks.[2]

Efficacy of TEDFIDERA compared with placebo was demonstrated across multiple domains.[1,2]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

RESULTS FROM THE 2-YEAR CONFIRM* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Annualized relapse rate (ARR)[1†]

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TECFIDERA 29%
(P=0.0020)

34% RELATIVE RISK REDUCTION

align

71% of TECFIDERA patients were free of relapse at 2 years

In CONFIRM, the reduction in the proportion with disability progression[‡] was not statistically significant[1]

Placebo 17%
TECFIDERA 13%
(P=0.25)

21% RELATIVE RISK REDUCTION

87% of TECFIDERA patients had no disability progression at 2 years

TECFIDERA n=359; Placebo n=363

Mean number of Gd+ lesions at 2 years[1]

Placebo 2.0
TECFIDERA 0.5
(P<0.0001)

74% RELATIVE ODDS REDUCTION

Mean number of new or newly enlarging T2 lesions over 2 years[1,2]

Placebo 17.4
TECFIDERA 5.1
(P<0.0001)

71% RELATIVE REDUCTION

align

Mean number of new T1 lesions over 2 years[1,2]

Placebo 7.0
TECFIDERA 3.0
(P<0.0001)

57% RELATIVE REDUCTION

TECFIDERA n=147; Placebo n=144

Gd+=gadolinium enhancing.
*Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis.[2]
†Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.[2]
‡Disability progression was defined as at least a 1-point increase from baseline Expanded Disability Status Scale (EDSS) of ≥1.0 or at least a 1.5-point increase for patients with baseline EDSS of 0 sustained for 12 weeks.[2]

Efficacy of TEDFIDERA compared with placebo was demonstrated across multiple domains.[1,2]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

Yes

These lines not in IVA. Ok as is?

OK bc there is a footnote

ARR and PPR called out above. Spell out here? Matches IVA as is.

remove bold

SD
REF
PI
ISI

RESULTS FROM THE 2-YEAR CONFIRM* TRIAL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Annualized relapse rate (ARR)[1†]

Placebo 0.401
TECFIDERA 0.224
(P<0.0001)

44% RELATIVE REDUCTION

Proportion of patients relapsed (PPR)[1†]

Placebo 41%
TECFIDERA 29%
(P=0.0020)

34% RELATIVE RISK REDUCTION

In CONFIRM, the reduction in the proportion with disability progression‡ was not statistically significant[1]

Placebo 17%
TECFIDERA 13%
(P=0.25)

21% RELATIVE RISK REDUCTION

TECFIDERA was associated with a 78% annualized relapse-free rate

71% of TECFIDERA patients were free of relapse at 2 years

87% of TECFIDERA patients had no disability progression at 2 years

TECFIDERA n=359; Placebo n=363

Mean number of Gd+ lesions at 2 years[1]

74% RELATIVE ODDS

Mean number of new or newly enlarging T2 lesions over 2 years[1,2]

Placebo 17.4
TECFIDERA 5.1
(P<0.0001)

71% RELATIVE

Mean number of new T1 lesions over 2 years[1,2]

Placebo 7.0
TECFIDERA 3.0
(P<0.0001)

57% RELAT

across multiple domains.[1,2]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

References

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
2. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis [published correction appears in *N Engl J Med*. 2012;367(17):1673]. *N Engl J Med*. 2012;367(12):1087-1097.

CONTRAINDICATION, ANAPHYLAXIS AND ANGIOEDEMA, AND PML

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Warnings and precautions

Delete per backup

- TECFIDERA is contraindicated in patients with known hypersensitivity to dimethly fumarate or to any of the exipients of TECFIDERA. Reactions have included anaphylaxis and angioedema[1]

Not in IVA

	Background	Signs and Symptoms	Directions for Patients
Anaphylaxis and angioedema	Can occur after the first dose or anytime during treatment with TECFIDERA	Include difficulty breathing, urticaria, and swelling of the throat and tongue	Discontinue TECFIDERA and seek immediate medical care
Progressive multifocal leukoencephalopathy (PML)[1]	A [illegible] occur in a patient who received TECFIDERA	Symptoms are diverse and progress over days to weeks	Discontinue TECFIDERA and seek immediate medical care
		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	

IVA says "Lymphopenia"

CS: please adivse

SAFETY

- Contraindication, Anaphylaxis and Angioedema, and PML
- Lymphocyte Counts
- Flushing
- Adverse Reactions
- Pregnancy

REF

PI

ISI

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

CONTRAINDICATION, ANAPHYLAXIS AND ANGIOEDEMA, AND PML

Should Header be all green?

Yes, all headers should be the same color per comment on backup

If this is removed from nav, remove here.

Delete

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

align

Warnings and precautions

IVA has "Contraindication" here and "Warnings and precautions" as subhead above table.

Change as indicated

- TECFIDERA is contraindicated in patients with known hypersensitivity to dimethly fumarate or to any of the exipients of TECFIDERA. Reactions have included anaphylaxis and angioedema[1]

c

Change

IVA says "Warning"

Background	Signs and Symptoms	Directions for Patients
Anaphylaxis and angioedema[1]	Can occur after the first dose or anytime during treatment with TECFIDERA	Include difficulty breathing, urticaria, and swelling of the throat and tongue	Discontinue TECFIDERA and seek immediate medical care
Progressive multifocal leukoencephalopathy (PML)[1]	A fatal case of PML occurred in a patient who received TECFIDERA	Symptoms are diverse and progress over days to weeks	Discontinue TECFIDERA and seek immediate medical care
		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	

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF

PI

ISI

CONTRAINDICATION, ANAPHYLAXIS AND ANGIOEDEMA, AND PML

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Warnings and precautions

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	Background	Signs and Symptoms	Directions for Patients
Anaphylaxis and angioedema[1]	Can occur after the first dose or anytime during treatment with TECFIDERA	Include difficulty breathing, urticaria, and swelling of the throat and tongue	Discontinue TECFIDERA and seek immediate medical care
Progressive multifocal leukoencephalopathy	A fatal case of PML occurred in a patient who received TECFIDERA	Symptoms are diverse and progress over days to weeks	Discontinue TECFIDERA and seek immediate medical care

Reference

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

TECFIDERA MAY LOWER LYMPHOCYTE COUNTS

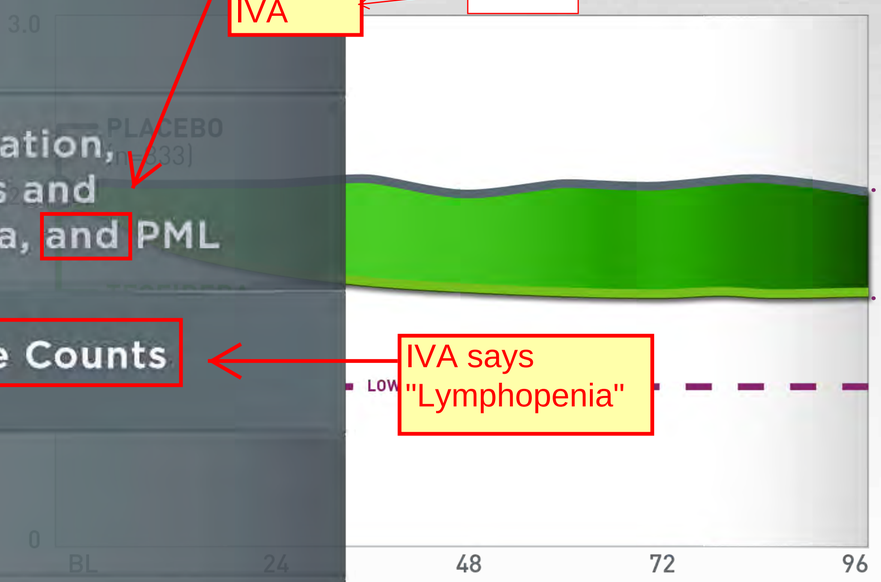
Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Warnings and precautions

MEAN LYMPHOCYTE COUNTS[1]

Not in IVA

Delete



IVA says "Lymphopenia"

During the first year, mean lymphocyte counts increased by approximately 30% and then remained stable[2]

- Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but did not return to baseline[2]
- Six percent [6%] of TECFIDERA patients and <1% of placebo patients experienced lymphocyte counts <0.5x10⁹/L (lower limit of normal 0.91x10⁹/L)[2]
- In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts <0.5 x 10⁹/L for at least six months. In these patients, the majority of lymphocyte counts remained <0.5x10⁹/L with continued therapy[2]

- TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts[2]
- Before initiating treatment with TECFIDERA, a recent complete blood cell count (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[2]
- Consider interruption of TECFIDERA in patients with lymphocyte counts <0.5 x 10⁹/L persisting for more than 6 months[2]
- Given the potential for delay in lymphocyte recovery after discontinuation of TECFIDERA, consider following lymphocyte counts until lymphopenia is resolved[2]

- The incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with TECFIDERA or placebo, respectively[2]
- There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 x 10⁹/L or 0.5 x 10⁹/L in controlled trials, although one patient developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly <0.5 x 10⁹/L for 3.5 years)[2]
- Decisions about whether or not to restart TECFIDERA should be individualized based on clinical circumstances[2]

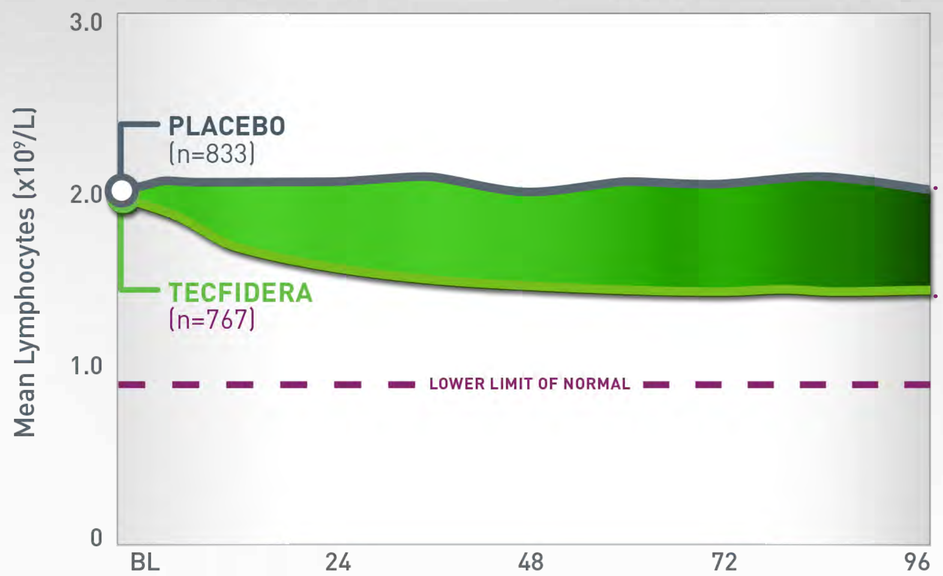
Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

TECFIDERA MAY LOWER LYMPHOCYTE COUNTS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Warnings and precautions

MEAN LYMPHOCYTE COUNTS[1]



Add label for x axis: Visit (Weeks)

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Add space around x per below.

one word

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run up

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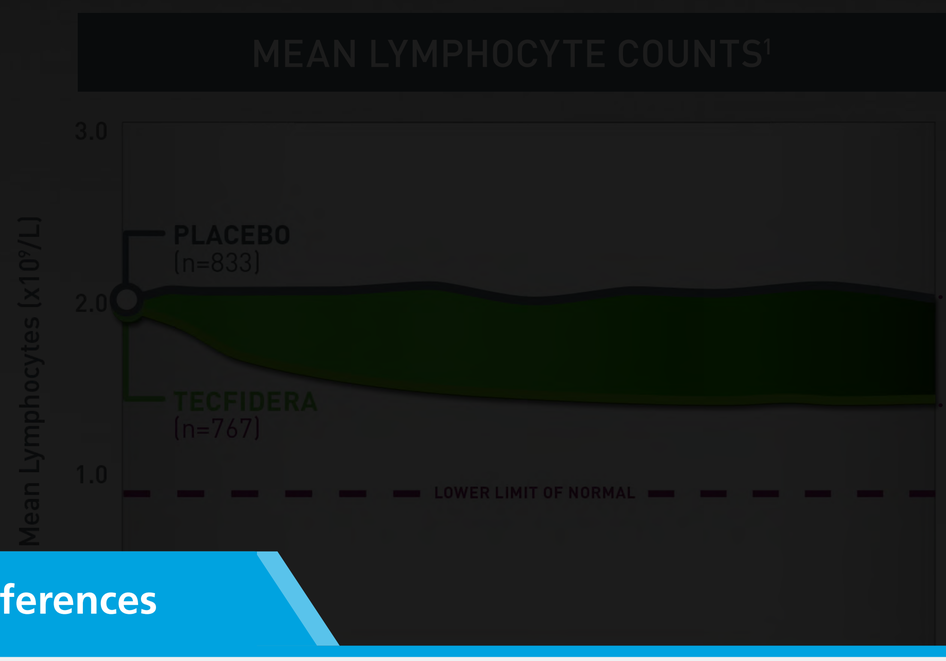
add: in an extension study

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

TECFIDERA MAY LOWER LYMPHOCYTE COUNTS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Warnings and precautions



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Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

References

1. Biogen, Data on file.
2. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.

REF

PI

ISI

FLUSHING

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Warnings and precautions

- TECFIDERA may cause flushing. In clinical trials, 40% experienced flushing
- Flushing symptoms generally began soon after initiating treatment and usually improved or resolved over time[1]
- 3% of patients discontinued TECFIDERA because of flushing and 1% had serious flushing symptoms that were not life-threatening but led to hospitalization[1]

SAFETY

Contraindication, Anaphylaxis and Angioedema, and PML

Not in IVA

Lymphocyte Counts

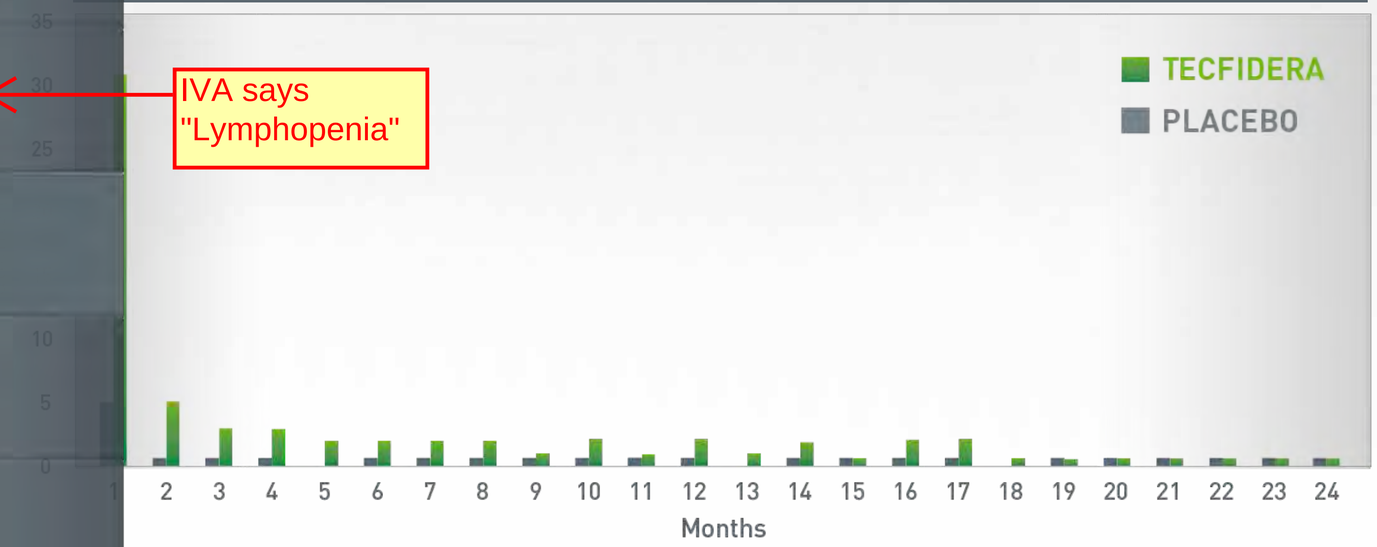
IVA says "Lymphopenia"

Flushing

Adverse Reactions

Pregnancy

INCIDENCE OF FLUSHING AND OTHER RELATED SYMPTOMS BY 1-MONTH INTERVALS[2]



Flushing consists of the preferred terms of flushing and hot flush. Other related symptoms consist of the preferred terms of erythema, generalized erythema, burning sensation, skin burning sensation, feeling hot, and hyperemia.[2]

TECFIDERA may cause flushing.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF

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ISI

FLUSHING

This should be green

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

align

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delete calll-out

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REF

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ISI

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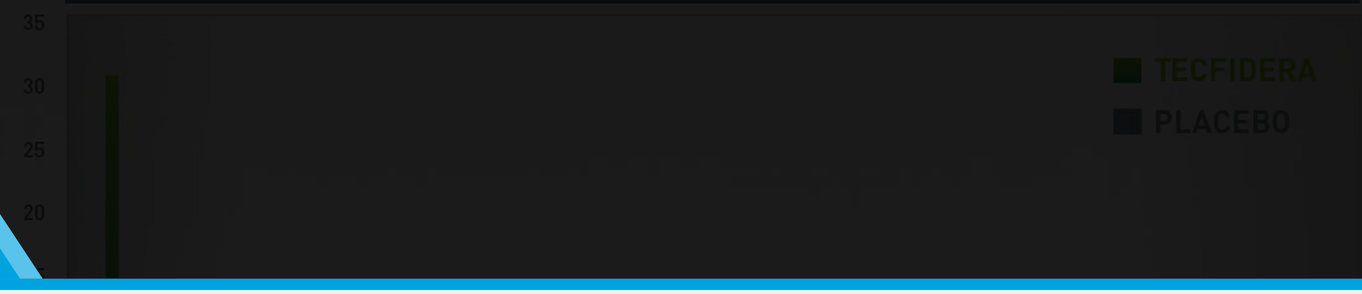

References

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
2. Biogen, Data on file.

the
ng hot,

TECFIDERA may cause flushing.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF
PI
ISI

ADVERSE REACTIONS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Adverse Reactions Reported for TECFIDERA 240 mg BID at ≥2% Higher Incidence Than Placebo[1]	TECFIDERA (n=769)	Placebo (n=771)
Blood and Lymphatic System Disorders		
Lymphopenia	2%	<1%
Gastrointestinal (GI) Disorders		
Abdominal pain	18%	10%
Diarrhea	14%	11%
Nausea	12%	9%
Vomiting	9%	5%
Dyspepsia	5%	3%
Vascular Disorders		
Flushing	40%	6%
Skin and Subcutaneous Tissue Disorders		
Pruritus	8%	4%
Rash	8%	3%
Erythema	5%	1%
Investigations		
Albumin urine present	6%	4%
Aspartate aminotransferase increased	4%	2%

Not in IVA

IVA says "Lymphopenia"

OVERALL DISCONTINUATION

GI EVENTS

HEPATIC TRANSAMINASES

The most common adverse reactions (incidence ≥10%, and ≥2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

ADVERSE REACTIONS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

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Replace this table with the Adverse Reactions table on pg 40 of IVA.

OVERALL DISCONTINUATION

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Abdominal pain	18%	10%
Diarrhea	14%	11%
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Vomiting	9%	5%
Dyspepsia	5%	3%
[illegible] disorders		
[illegible]	40%	6%

OVERALL DISCONTINUATION

GI EVENTS

The most common adverse reactions (incidence ≥10%, and ≥2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

Reference

1. TECFIDERA [Prescribing Information], Cambridge, MA: Biogen, Decemeber 2014.

REF

PI

ISI

OVERALL DISCONTINUATION

Can we enlarge the circles or change the shapes so that the line breaks/bolding is a little cleaner?

Approximately **70%** of patients treated with **TECFIDERA BID** completed **96 weeks** of treatment (compared with **65%** of patients taking placebo) in **2 clinical trials**[1]

Discontinuation rates due to an adverse reaction with **TECFIDERA** were **14%** vs **11%** for placebo in **2 clinical trials**[2]

Add call-out box per backup:
Approximately 70% of TECFIDERA patients and 65% of placebo patients completed 96 weeks of treatment.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF
PI
ISI

OVERALL DISCONTINUATION

Approximately **70%** of patients treated with **TECFIDERA BID** completed **96 weeks** of treatment (compared with **65%** of patients taking

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References

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
2. Biogen, Data on file.

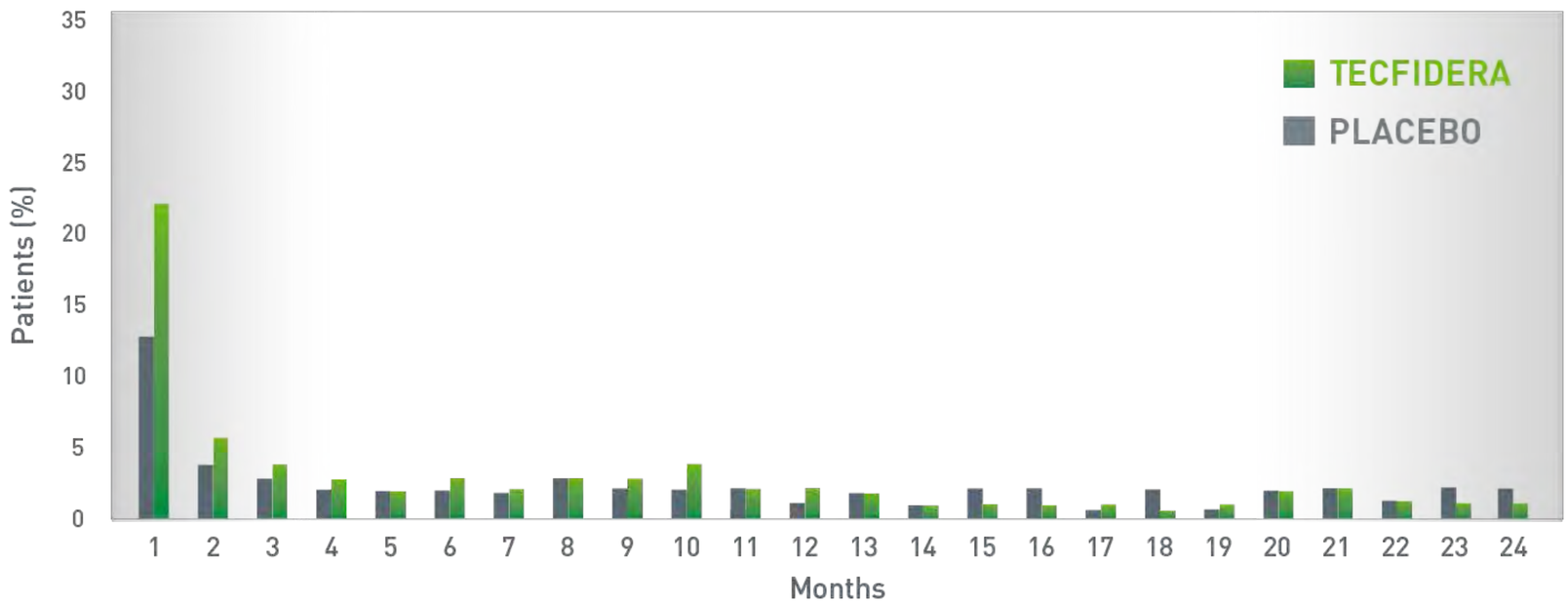
Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF
PI
ISI

GASTROINTESTINAL EVENTS

- TECFIDERA caused gastrointestinal (GI) events. The incidence of GI events was higher early in treatment and usually decreased over time[1]
- 4% of patients taking TECFIDERA discontinued due to GI events vs <1% of placebo patients[1]
- 1% of TECFIDERA patients experienced serious GI events[1]

INCIDENCE OF GI EVENTS BY 1-MONTH INTERVALS[2]



Add copy per IVA: GI events included nausea, diarrhea, abdominal pain, and/or upper abdominal pain.[2]

Add call-out box per backup: TECFIDERA may cause GI events.

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF
PI
ISI

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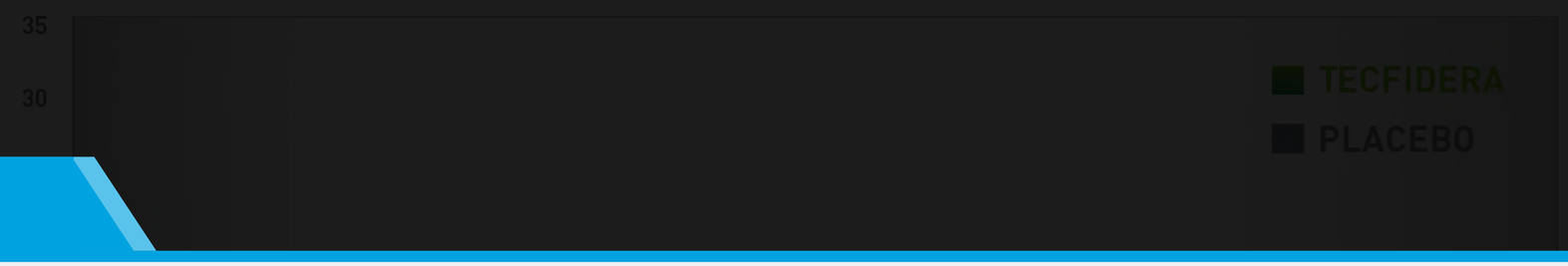

References

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
2. Biogen, Data on file.

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF
PI
ISI

ELEVATIONS OF HEPATIC TRANSAMINASES

Elevations of hepatic transaminases were primarily seen during the first 6 months of treatment and occurred at levels <3 times the upper limit of normal (ULN)[1]

delete space before ref no.

The majority of patients with elevations had levels that were <3 times the ULN[1]

Discontinuations due to elevated hepatic transaminases were <1% and were similar in patients treated with TECFIDERA or placebo[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF

PI

ISI

ELEVATIONS OF HEPATIC TRANSAMINASES

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Reference

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Change to blue

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

REF

PI

ISI

PREGNANCY

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

SAFETY

Contraindication, Anaphylaxis and Angioedema, and PML

Lymphocyte Counts

Flushing

Adverse Reactions

Pregnancy

Not in IVA

IVA says "Lymphopenia"

align Flushing and Pregnancy

TECFIDERA is in Pregnancy Category C[1]

There are no adequate or well-controlled studies in pregnant women[1]

TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus[1]

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[1]

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[1]

REF

PI

ISI

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

PREGNANCY

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

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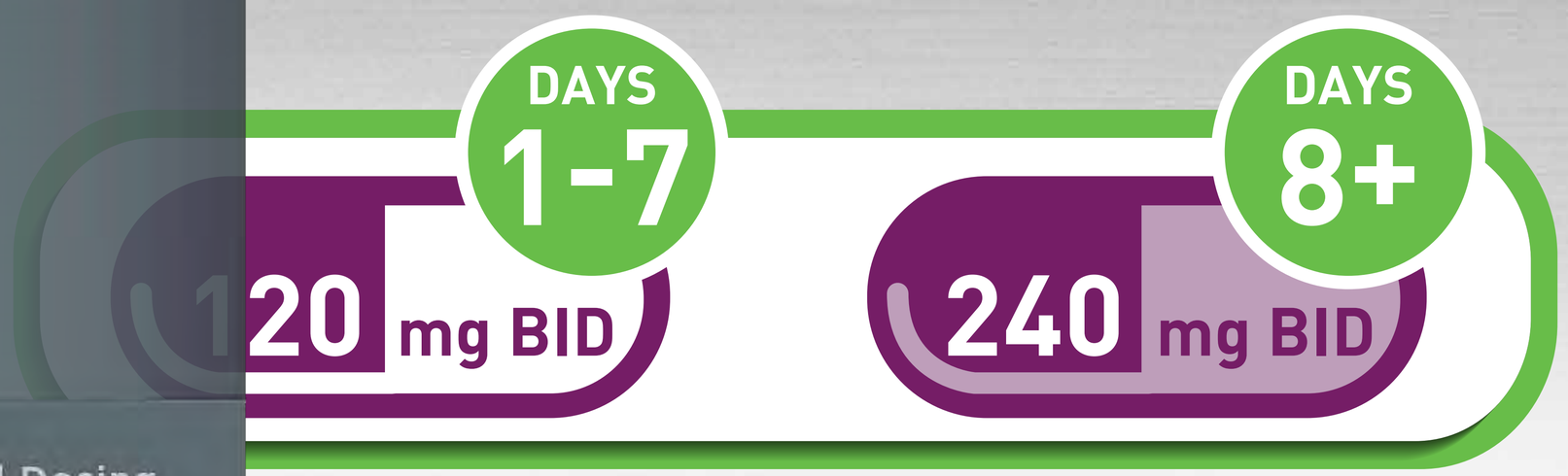
ISI

TWICE-DAILY ORAL DOSING

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg



TECFIDERA is administered via oral dosing

- The starting dose of TECFIDERA is one 120-mg capsule BID (Days 1-7), and the maintenance dose is one 240-mg capsule BID after Day 7[1]
- TECFIDERA should be swallowed whole and intact
- TECFIDERA should not be crushed or chewed, and the capsule contents should not be sprinkled on food
- Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose[1]
  - Within 4 weeks, the recommended dose of 240 mg twice a day should be resumed[1]
  - Discontinuation of TECFIDERA should be considered for patients unable to tolerate return to the maintenance dose[1]

Compared with parenteral multiple sclerosis treatments, TECFIDERA may provide convenience, ease of use, and the elimination of injection administration-site pain.[1]

Please see full Prescribing Information and Important Safety Information, accessible from the left-hand navigation bar.

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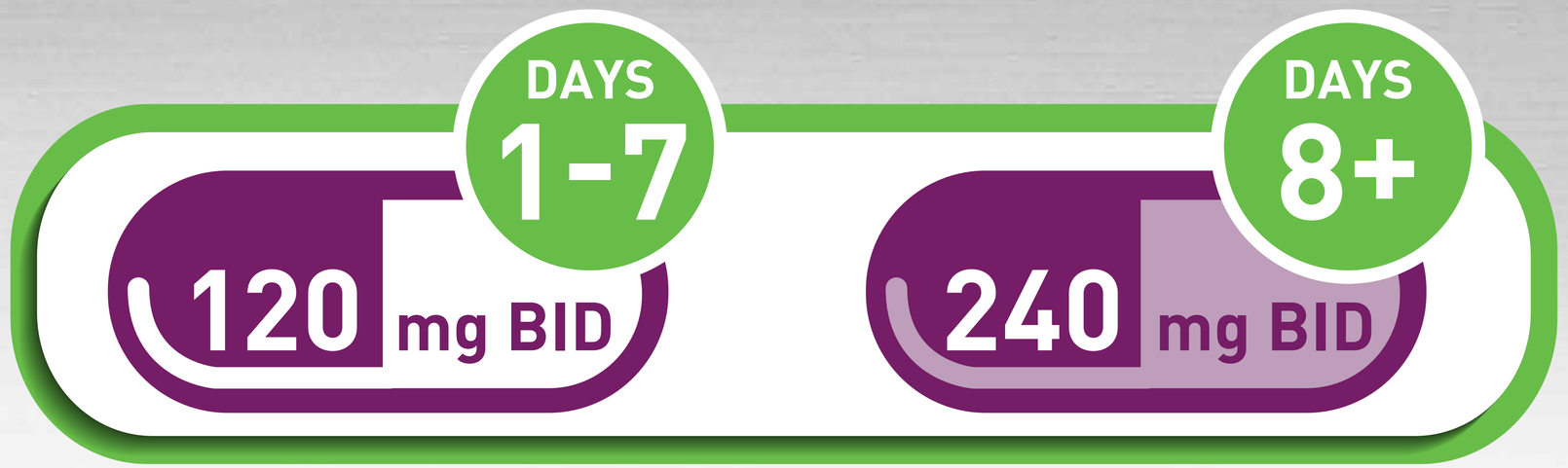

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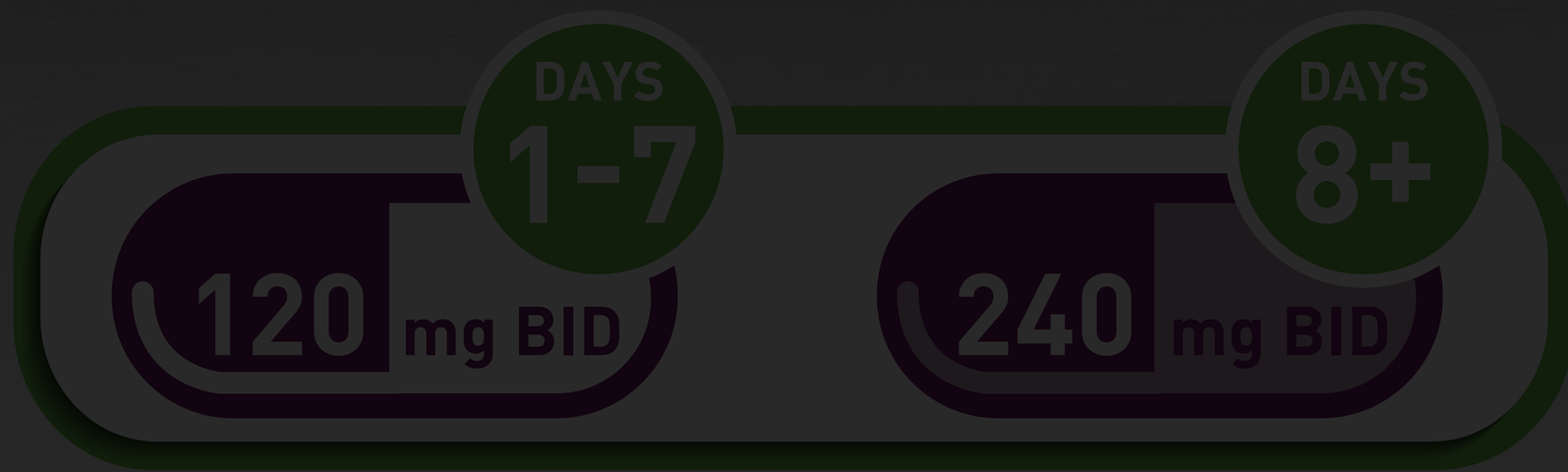

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food

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References

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GROWING REAL-WORLD EXPERIENCE ACCESS FOR MEMBERS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

MORE THAN 5 YEARS OF COMBINED CLINICAL AND REAL-WORLD EXPERIENCE[1,2]

#1 PRESCRIBED ORAL THERAPY FOR RELAPSING MS IN THE US SINCE SEPTEMBER 2013*

NOW MORE THAN 135,000 PATIENTS GLOBALLY HAVE BEEN TREATED WITH TECFIDERA[2]

>90% FORMULARY COVERAGE[1]

*Based on number of prescriptions from IMS NPA™ Weekly Data (October 11-17, 2013).[3]

ABOVE MS™ is a patient service resource connecting your members with assistance, support, and community.

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GROWING REAL-WORLD EXPERIENCE ACCESS FOR MEMBERS

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MORE THAN **5** YEARS OF COMBINED CLINICAL AND REAL-WORLD EXPERIENCE[1,2]

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add circle with "**MORE THAN 8000** have prescribed TECFIDERA in the United States[2]

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References

1. TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.
2. Biogen, Data on file.
3. Fingertip Formulary®. March 2015.

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TECFIDERA BUDGET IMPACT MODEL

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

Estimating the cost impact of TECFIDERA on a health plan

- Informs formulary decision-makers about treatment acquisition costs and administration and monitoring costs of up to 11 possible disease-modifying therapies for relapsing multiple sclerosis (RMS) in a health plan population
- fic demographics, market share information, prevalence and treatment rates RMS, benefit design, copays, coinsurance, administration and monitoring costs, uisition costs for the mix of agents used in treating this patient population
- Does not include costs associated with managing adverse events and relapse

Intended only for distribution to members of formulary committees or similar entities pursuant to Section 114 of the FDA Modernization Act.

To learn more about the TECFIDERA Budget Impact Model, please contact your Biogen Health Economics and Outcomes Research Representative.

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Do we have an image for this or should we delete and move up copy?

- Informs formulary decision-makers about treatment acquisition costs and administration and monitoring costs of up to 11 possible disease-modifying therapies for relapsing multiple sclerosis (RMS) in a health plan population
- Utilizes plan-specific demographics, market share information, prevalence and treatment rates for members with RMS, benefit design, copays, coinsurance, administration and monitoring costs, and wholesale acquisition costs for the mix of agents used in treating this patient population
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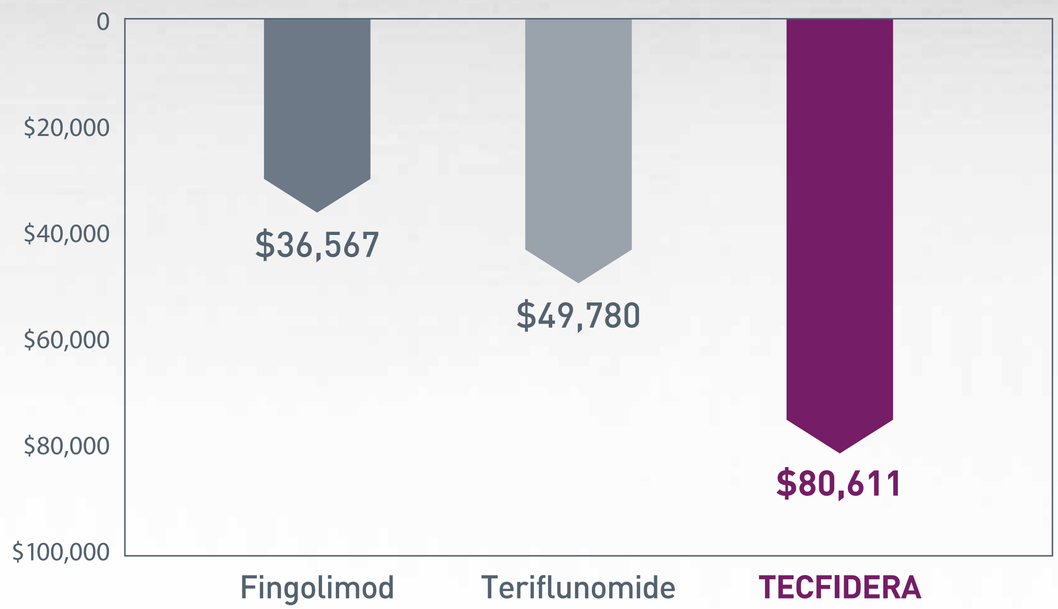
TECFIDERA IS A COST-EFFECTIVE OPTION FOR THE TREATMENT OF REPLAPSING MULTIPLE SCLEROSIS

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

- In a cost-effectiveness analysis that compared TECFIDERA, fingolimod, and teriflunomide with intramuscular (IM) interferon (IFN)-β1a for the treatment of relapsing multiple sclerosis (RMS), all 3 oral therapies were found to be more cost-effective than IM IFN-β1a[1]
- TECFIDERA dominated all other therapies studied over the range of willingness-to-pay values from US$0 to US$180,000 for patients[1]

ESTIMATED INCREMENTAL NET MONETARY BENEFIT OVER 5 YEARS OF ORAL DISEASE-MODIFYING THERAPIES VS IM IFN-β1a AT A WILLINGNESS-TO-PAY VALUE OF US $150,000[1]*



tribution to members of formulary committees or similar entities pursuant to Section 114 ation Act.

*The analysis compared TECFIDERA 120 mg BID for the first 7 days and 240 mg BID after 7 days, fingolimod (0.5 mg once daily), and teriflunomide (14 mg once daily) with IFN-β_{1a} (30 µg/week). Costs were modeled on the basis of stratified Expanded Disability Status Scale (EDSS) scores. Costs in the analysis included hospital inpatient care, ambulatory care, tests, drugs (disease-modifying drugs and other drugs), services, adaptations, and informal care. Productivity losses were not included.[1]

TECFIDERA is a cost-effective, first-line therapy in the treatment of patients with RMS.[1]

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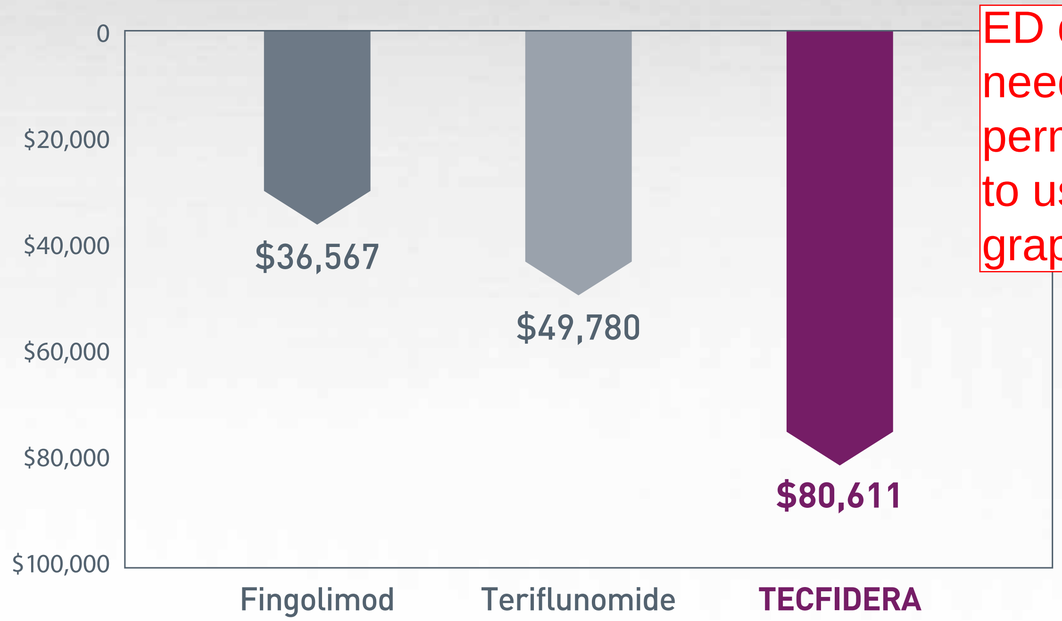

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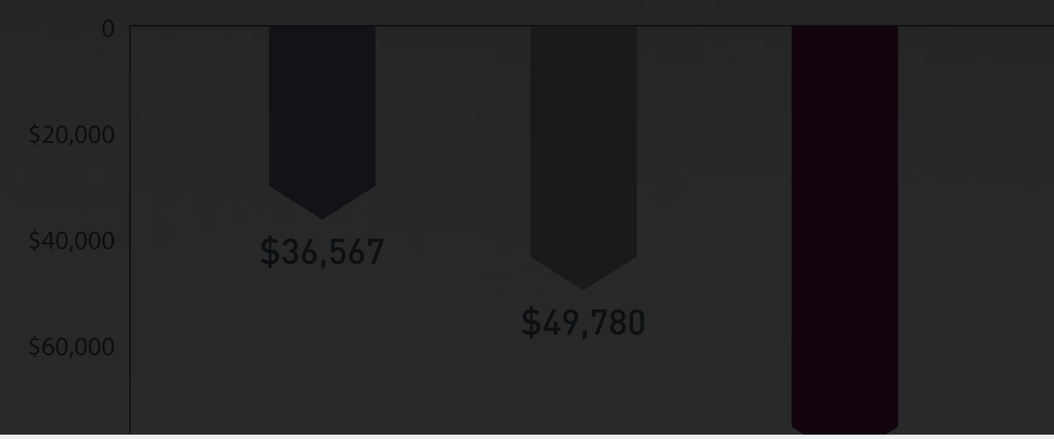

Reference

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1. Zhang X, Hay JW, Niu X. Cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate and intramuscular interferon-β1a in relapsing-remitting multiple sclerosis. *CNS Drugs.* 2015;29(1):71-81.

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SUMMARY

Tecfidera® (dimethyl fumarate) delayed-release capsules 240 mg

- In phase 3 studies, TECFIDERA was evaluated in both treatment-naïve and treatment-experienced patients[1,2]
- Compared with placebo, TECFIDERA demonstrated significant improvements across multiple outcomes[1-3]
  - Relapse rates
  - Disability progression
  - Magnetic resonance imaging findings
- TECFIDERA may cause anaphylaxis and angioedema, progressive multifocal leukoencephalopathy, lymphopenia, and flushing[3]
- TECFIDERA is the #1-prescribed oral therapy for relapsing multiple sclerosis (RMS) in the United States since September 2013[4]
- The most common adverse reactions (incidence ≥10% and ≥2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea[3]
- TECFIDERA is a cost-effective, first-line therapy in the treatment of patients with RMS[5]

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2. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis [published correction appears in *N Engl J Med*. 2012;367(24):2362]. *N Engl J Med*. 2012;367(12):1098-1107.
3. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis [published correction appears in *N Engl J Med*. 2012;367(17):1673]. *N Engl J Med*. 2012;367(12):1087-1097.
4. ~~TECFIDERA [Prescribing Information]. Cambridge, MA: Biogen; December 2014.~~
5. Zhang X, Hay JW, Niu X. Cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate and intramuscular interferon-β1a in relapsing-remitting multiple sclerosis. *CNS Drugs*. 2015;29(1):71-81.
6. Biogen, Data on file.

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