PRODUCT MONOGRAPH

Pr TECFIDERA®

Dimethyl fumarate delayed-release capsules

120 mg and 240 mg

Other Nervous System Drug

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Pr TECFIDERA®

Dimethyl fumarate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Delayed-release capsules / 120 mg and 240 mg	Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, methacrylic acid copolymer (type A), methacrylic acid copolymer dispersion, microcrystalline cellulose, polysorbate 80, silicified microcrystalline cellulose, simethicone, sodium lauryl sulfate, talc, and triethyl citrate. The capsule shell contains black iron oxide, FD&C Blue 1, gelatin, titanium dioxide, and yellow iron oxide.

INDICATIONS AND CLINICAL USE

Adults:
TECFIDERA (dimethyl fumarate) is indicated as monotherapy for the treatment of relapsing remitting multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the progression of disability.

The efficacy of TECFIDERA in patients with primary progressive multiple sclerosis has not been established.

TECFIDERA should only be prescribed by clinicians who are experienced in the diagnosis and management of multiple sclerosis.

Geriatrics (> 65 years of age):
Clinical studies of TECFIDERA did not include sufficient numbers of patients aged 65 and over to determine whether the safety and efficacy of TECFIDERA may differ in elderly patients compared to younger patients. Physicians who choose to treat geriatric patients should consider that treatment with TECFIDERA in the context of a greater frequency of other concomitant diseases and concomitant drug therapy warrants caution and may necessitate additional or more frequent monitoring (see WARNINGS AND PRECAUTIONS, Special Populations - Geriatrics).

Pediatrics (< 18 years of age):
The safety and efficacy of TECFIDERA in patients younger than 18 years of age have not been evaluated. TECFIDERA is not indicated in patients below 18 years of age.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see POST MARKET ADVERSE DRUG REACTIONS). For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General
During treatment with TECFIDERA, simultaneous use of other fumaric acid derivatives (topical or systemic) is not recommended.

Progressive Multifocal Leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with TECFIDERA, in the presence of prolonged, moderate to severe lymphopenia, including in patients who had not previously taken or were not concomitantly taking either immunosuppressive or immunomodulatory medications (see Adverse Reactions, Post-Marketing Experience). 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 may lead to death or severe disability.

Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, TECFIDERA treatment should be suspended until PML has been excluded. 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.

There is no known intervention that can reliably prevent PML or adequately treat PML if it occurs. Lymphocyte counts should be monitored in patients taking TECFIDERA and as a precaution, interruption of TECFIDERA should be considered in patients with lymphocyte counts $<0.5 \times 10^9$/L persisting for more than 6 months (see WARNINGS AND PRECAUTIONS, Hematologic).

Hematologic
TECFIDERA (dimethyl fumarate) may decrease lymphocyte counts (see ADVERSE DRUG REACTIONS, Abnormal Hematologic and Clinical Chemistry findings). In the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with TECFIDERA then remained stable at this reduced level for the duration of treatment. Six percent (6%) of TECFIDERA patients and < 1% of placebo patients experienced lymphocyte counts $< 0.5 \times 10^9$/L (lower limit of normal 0.91×10^9/L). In controlled and uncontrolled clinical trials, 9% of patients had lymphocyte counts $\geq 0.5 \times 10^9$/L and $<0.8 \times 10^9$/L for at least six months. 2% of patients experienced lymphocyte counts $<0.5 \times 10^9$/L for at least 6 months and in this group, the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy.

Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but did not return to baseline. The time to recovery to baseline lymphocyte counts has not been established.

The following precautions should be taken:

- Prior to initiating treatment with TECFIDERA, obtain a complete blood count (CBC), including lymphocytes, if no recent (within 6 months) result is available. A CBC, including lymphocytes, is also recommended after 6 months of treatment, then every 6 to 12 months, and as clinically indicated.
- Consider interruption of TECFIDERA in patients with lymphocyte counts $<0.5 \times 10^9/L$ persisting for more than 6 months. Given that the time to lymphocyte recovery has not been established, lymphocyte counts should be followed until recovery.
- Assess the benefit-risk in patients that experience moderate lymphopenia for more than 6 months.
- A CBC is also recommended prior to switching patients to other therapies that are known to reduce lymphocyte counts to avoid additive immune effects (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).
- Patients with pre-existing low lymphocyte counts, and patients concomitantly taking other immunomodulating treatments, were excluded from the multiple sclerosis clinical trials. Treatment is not recommended in patients who are immunocompromised due to other treatments (e.g., anti-neoplastic, immunosuppressive or immune modulating therapies) or disease (e.g., immunodeficiency syndrome), due to the potential risk of additive immune system effects.

Vascular Disorders

TECFIDERA may cause flushing (e.g. flushing, hot flush, warmth, redness, itching, and/or burning sensation). In placebo controlled clinical trials in patients with multiple sclerosis, 34% of TECFIDERA treated patients, compared to 5% of patients that received placebo, experienced flushing. Flushing symptoms generally began soon after initiating TECFIDERA and usually improved or resolved over time (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions). In the majority of patients who experienced flushing, it was mild or moderate in severity. For patients experiencing severe flushing reactions the possibility of hypersensitivity or anaphylactoid reactions should be considered (see WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity; ADVERSE REACTIONS, Post Market Adverse Reactions).

Administration of TECFIDERA with food, administration of 325 mg non-enteric coated acetylsalicylic acid prior to dosing, or a temporary dose reduction to 240 mg/day may reduce the incidence of flushing (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment). The long-term use of acetylsalicylic acid is not recommended for the management of flushing (see DRUG INTERACTIONS).

Gastrointestinal Disorders

TECFIDERA may cause gastrointestinal adverse events. In placebo controlled clinical trials in patients with multiple sclerosis, 48% of patients treated with TECFIDERA compared to 36% of patients that received placebo, experienced gastrointestinal adverse events. The increased frequency of gastrointestinal adverse events with TECFIDERA was mainly due to higher frequencies of nausea, vomiting, diarrhea, abdominal pain, upper abdominal pain, and dyspepsia. Gastroenteritis was also

reported more frequently in patients treated with TECFIDERA than in patients who received placebo (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

Administration of TECFIDERA with food or a temporary dose reduction to 240 mg/day may improve tolerability in patients who experience gastrointestinal adverse events (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

TECFIDERA has not been evaluated in patients with severe active gastrointestinal disease and caution should be exercised when treating these patients.

Immune

Infections: Treatment with TECFIDERA should not be initiated in patients with signs and symptoms of a serious infection.

Decreases in lymphocyte counts observed in patients treated with TECFIDERA in clinical trials were not associated with increased frequencies of infections. However, due to the potential risk of infections in patients who develop sustained lymphopenia, patients should be instructed to report symptoms of infection to their physician. For patients with signs and symptoms of serious infections, interrupting treatment with TECFIDERA should be considered, until the infection(s) resolves.

Vaccination: The safety of administration of live attenuated vaccines during treatment with TECFIDERA has not been evaluated in clinical trials. Live vaccines have a potential risk of clinical infection and are not recommended during treatment with TECFIDERA.

The efficacy of vaccines administered during treatment with TECFIDERA has not been evaluated in clinical trials.

Hypersensitivity: In clinical trials, 3 patients out of a total of 2,560 patients treated with TECFIDERA experienced serious flushing symptoms that were probable hypersensitivity or anaphylactoid reactions. These events were not life-threatening, but led to hospitalization. Cases of hypersensitivity, angioedema and anaphylactic reaction have been reported during the post marketing period (see ADVERSE REACTIONS, Post Market Adverse Drug Reactions). Prescribers and patients should be alert to this possibility in the event of severe flushing reaction. Patients should be instructed to discontinue TECFIDERA and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema.

Hepatic/Biliary

During clinical trials in patients with multiple sclerosis, elevations in liver transaminases (ALT and AST) > 1 x the upper limit of normal (ULN) and less than 3 x ULN occurred more frequently in patients treated with TECFIDERA than in patients that received placebo. The increased incidence of elevations of hepatic transaminases in patients treated with TECFIDERA relative to placebo was primarily seen during the first 6 months of treatment (see ADVERSE REACTIONS, Hepatic Transaminases).

Prior to initiating treatment with TECFIDERA, serum aminotransferase, alkaline phosphatase and total bilirubin levels should be obtained (within 6 months). During treatment, evaluation of transaminases is

recommended after 6 months of treatment, then every 6 to 12 months, and as clinically indicated. Discontinue TECFIDERA if clinically significant liver injury induced by TECFIDERA is suspected.

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

Renal

In clinical trials with patients with multiple sclerosis, adverse events of proteinuria (proteinuria, microalbuminuria and urine albumin present) were reported at slightly higher frequencies in patients treated with TECFIDERA compared to patients that received placebo. The significance of these clinical observations is not known at this time.

Prior to initiating treatment with TECFIDERA, urinalysis should be available (within 6 months). During treatment, urinalysis is recommended after 6 months of treatment, then every 6 to 12 months, and as clinically indicated.

The use of TECFIDERA in patients who receive chronic treatment with medications that are associated with potential nephrotoxic risk (e.g., aminoglycosides, diuretics, NSAIDs, lithium) has not been evaluated. Therefore, caution should be exercised if TECFIDERA is used in patients receiving chronic treatment with such medications.

Special Populations

Hepatic Impairment: The safety of TECFIDERA has not been evaluated in patients with hepatic impairment and it is not known if these patients are at an increased risk of developing elevated liver transaminases, or other adverse events during treatment with TECFIDERA. Caution should be exercised when treating these patients (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary; WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings; DOSAGE AND ADMINISTRATION, Dosing Considerations).

Renal Impairment: The safety of TECFIDERA has not been evaluated in patients with renal impairment and it is not known if these patients are at an increased risk of developing renal adverse events, or other adverse events during treatment with TECFIDERA. Caution should be exercised when treating these patients (see WARNINGS AND PRECAUTIONS, Renal, Monitoring and Laboratory Tests; ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Abnormal Hematologic and Clinical Chemistry Findings; DOSAGE AND ADMINISTRATION, Dosing Considerations).

Pregnant Women: There are no adequate and well-controlled studies of TECFIDERA in pregnant women. The use of TECFIDERA during pregnancy should only be considered if the potential benefit

to the mother justifies the potential risk to the fetus.

Monomethyl fumarate was detected in rat and rabbit fetal plasma after oral dimethyl fumarate administration to the mothers. Administration of dimethyl fumarate to rats and rabbits at doses up to 11 and 16 times the recommended human dose (RHD) (AUC basis), respectively, have revealed no evidence of ~~or~~ teratogenicity. There were no fertility effects in male and female rats at exposures of 9 and 6 times the RHD, respectively (based on mg/m2). Embryo-fetal toxicity that may have been secondary to maternal toxicity was observed when dimethyl fumarate was given during the period of organogenesis. Adverse effects were observed in offspring when dimethyl fumarate was administered during the pre- and post-natal periods, with the no effect dose at 4 times the RHD on an AUC basis (see TOXICOLOGY).

Nursing Women: It is not known whether dimethyl fumarate or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TECFIDERA is administered to a nursing woman.

Pediatrics (< *18* years of age): The safety and efficacy of TECFIDERA in patients younger than 18 years of age have not been evaluated. TECFIDERA is not indicated in patients below 18 years of age.

Geriatrics (> *65* years of age): Clinical studies of TECFIDERA did not include sufficient numbers of patients aged 65 and over to determine whether the safety and efficacy of TECFIDERA may differ in elderly patients compared to younger patients. Physicians who choose to treat geriatric patients should consider that treatment with TECFIDERA in the context of a greater frequency of other concomitant diseases and concomitant drug therapy warrants caution and may necessitate additional or more frequent monitoring (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations - Geriatrics).

Monitoring and Laboratory Tests

Prior to initiating treatment, a recent complete blood count (CBC), including lymphocytes, (i.e. within 6 months) is recommended to identify patients with pre-existing low lymphocyte counts, as TECFIDERA may decrease lymphocyte counts (see WARNINGS AND PRECAUTIONS, Hematologic; ADVERSE DRUG REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings). A CBC, including lymphocytes, is recommended after 6 months, then every 6 to 12 months, and as clinically indicated (see WARNINGS AND PRECAUTIONS, Hematologic; ADVERSE DRUG REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Urinalysis should be performed before initiating treatment with TECFIDERA, after 6 months of treatment, then every 6 to 12 months, and as clinically indicated (see WARNINGS AND PRECAUTIONS, Renal; ADVERSE DRUG REACTIONS, Clinical Trial Adverse Drug Reactions, Abnormal Hematologic and Clinical Chemistry Findings).

Liver transaminases should be checked (within 6 months) before initiating treatment with TECFIDERA. During treatment, evaluation of transaminases is recommended after 6 months of treatment, then every 6 to 12 months and as clinically indicated (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary; ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Patient Counselling Information

Consumer information is included in the package of TECFIDERA dispensed to the patient. Patients receiving TECFIDERA should also be given the following information by the physician and/or pharmacist:

1. ***General***
   Summarize for patients the benefits and potential risks of treatment with TECFIDERA. Tell patients to take TECFIDERA as prescribed. Tell patients not to discontinue TECFIDERA or switch to another therapy without first discussing this with the prescribing physician.

2. ***Lymphocyte count decreases***
   Inform patients that TECFIDERA may decrease lymphocyte counts. Advise patients that regular blood testing will be performed and that they should contact their physician if they develop symptoms of a serious infection (e.g. pneumonia).

3. ***Liver enzyme increases***
   Inform patients that TECFIDERA may increase liver enzymes. Advise patients that regular blood testing will be performed.

4. ***Protein in urine***
   Inform patients that TECFIDERA may increase protein in the urine. Advise patients that regular urine testing will be performed.

5. ***Pregnancy***
   Advise women of childbearing age about the use of effective contraception.

6. ***Anaphylactic reaction***
   Instructed patients to discontinue TECFIDERA and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema.

7. ***Common adverse events:***
   Flushing
   Inform patients that TECFIDERA may cause flushing and that it is most common soon after starting treatment. Advise them that taking TECFIDERA with food, temporary dose reduction or administration of 325 mg non-enteric coated acetylsalicylic acid prior to dosing may reduce the incidence of flushing. Advise patients acetylsalicylic acid should not be used long-term for the management of flushing. For patients experiencing severe flushing reactions the possibility of hypersensitivity or anaphylactoid reactions should be considered.

   Gastrointestinal events
   Inform patients that TECFIDERA may cause gastrointestinal events. Advise them that taking TECFIDERA with food or temporary dose reduction to 240 mg/day may improve tolerability.

8. ***Vaccination***
   Advise patients that the use of live attenuated vaccines is not recommended during treatment with TECFIDERA. The effectiveness of vaccines in patients taking TECFIDERA is unknown.

9. Drug interactions

Inform patients that during treatment with TECFIDERA, simultaneous use of other fumaric acid derivatives (topical or systemic) is not recommended. Advise patients that co-administration of anti-neoplastic, immunosuppressive or immune-modulating therapies is not recommended due to the potential risk of additive immune system effects.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the two Phase 3 placebo-controlled trials, 1529 patients received TECFIDERA (dimethyl fumarate) with an overall exposure of 2371 person years. The adverse reactions presented below are based on safety information from 769 patients treated with TECFIDERA 240 mg twice a day and 771 patients treated with placebo.

The most common adverse reactions (incidence > 10%) for patients treated with TECFIDERA were flushing and gastrointestinal (GI) events (i.e. diarrhea, nausea, abdominal pain and abdominal pain upper). In the majority of subjects, the adverse reactions were non-serious in nature. The most commonly reported adverse events leading to discontinuation of treatment (incidence > 1%) in patients treated with TECFIDERA were flushing (3%) and gastrointestinal events (4%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 lists treatment emergent adverse events that occurred during active treatment in ≥1% of TECFIDERA-treated patients and at ≥1% higher incidence than placebo in the two Phase 3 placebo-controlled trials.

Table 1 – Treatment-Emergent Adverse Events with an Incidence of ≥1% of TECFIDERA Treated Patients and at ≥1% Higher Rate than for Placebo

Adverse Event	Placebo N=771	TECFIDERA 240 mg BID N=769
Flushing	33 (4.3%)	265 (34.5%)
Nasopharyngitis	159 (20.6%)	170 (22.1%)
Diarrhea	83 (10.8%)	107 (13.9%)
Urinary Tract Infection	95 (12.3%)	107 (13.9%)
Upper Respiratory Tract Infection	87 (11.3%)	99 (12.9%)
Nausea	67 (8.7%)	93 (12.1%)
Abdominal Pain Upper	45 (5.8%)	76 (9.9%)
Abdominal Pain	37 (4.8%)	73 (9.5%)
Proteinuria	59 (7.7%)	67 (8.7%)

Adverse Event	Placebo N=771	TECFIDERA 240 mg BID N=769
Vomiting	37 (4.8%)	65 (8.5%)
Pruritus	30 (3.9%)	62 (8.1%)
Rash	26 (3.4%)	58 (7.5%)
Hot Flush	16 (2.1%)	52 (6.8%)
Albumin Urine Present	27 (3.5%)	46 (6.0%)
Alanine Aminotransferase Increased	38 (4.9%)	45 (5.9%)
Gastroenteritis	28 (3.6%)	42 (5.5%)
Erythema	10 (1.3%)	36 (4.7%)
Dyspepsia	20 (2.6%)	35 (4.6%)
Microalbuminuria	24 (3.1%)	35 (4.6%)
Aspartate Aminotransferase Increased	18 (2.3%)	33 (4.3%)
Gastritis	11 (1.4%)	22 (2.9%)
Burning Sensation	13 (1.7%)	21 (2.7%)
Abdominal Discomfort	11 (1.4%)	19 (2.5%)
Gastrointestinal Disorder	8 (1.0%)	18 (2.3%)
Lymphopenia	2 (0.3%)	18 (2.3%)
Blood Urine Present	7 (0.9%)	16 (2.1%)
Dry Mouth	6 (0.8%)	16 (2.1%)
Blood Parathyroid Hormone Increased	6 (0.8%)	15 (2.0%)
Feeling Hot	2 (0.3%)	15 (2.0%)
Rhinorrhoea	8 (1.0%)	15 (2.0%)
Dermatitis Allergic	5 (0.6%)	13 (1.7%)
White Blood Cell Count Decreased	1 (0.1%)	13 (1.7%)
Dysaesthesia	5 (0.6%)	12 (1.6%)
Hypersensitivity	2 (0.3%)	11 (1.4%)
Weight Decreased	3 (0.4%)	11 (1.4%)
Otitis Media	1 (0.1%)	10 (1.3%)
Lymphocyte Count Decreased	1 (0.1%)	9 (1.2%)

Flushing: In the placebo-controlled trials, 34% of TECFIDERA treated patients, compared to 5% of patients that received placebo, experienced flushing adverse events. The incidence of flushing adverse events (e.g. flushing, hot flush, warmth, redness, itching, burning sensation) was higher early in the course of treatment (primarily in month 1) and decreased over time. The majority of flushing adverse events were mild-to-moderate in severity. Overall, 3% of patients treated with TECFIDERA compared to < 1% on placebo discontinued treatment due to flushing. The incidence of serious flushing which may be characterized by generalized erythema, rash and/or pruritus was seen in less than 1% of patients treated with TECFIDERA (see WARNINGS AND PRECAUTIONS, Vascular and DOSAGE AND ADMINISTRATION).

Gastrointestinal: In placebo controlled clinical trials, 48% of patients treated with TECFIDERA compared to 36% of patients that received placebo, experienced gastrointestinal adverse events. The incidence of GI related adverse events (e.g. nausea, vomiting, diarrhea, abdominal pain, upper abdominal pain & dyspepsia) was higher early in the course of treatment (primarily in month 1) and usually decreased over time in patients treated with TECFIDERA compared with placebo. Four percent (4%) of patients treated with TECFIDERA and less than 1% of placebo treated patients discontinued due to gastrointestinal adverse events. The incidence of individual serious GI events, including gastroenteritis and gastritis, was less than 1% of patients treated with TECFIDERA (see WARNINGS AND PRECAUTIONS, Gastrointestinal Disorders and DOSAGE AND ADMINISTRATION)

Infections: The incidence of infections (60% vs. 56%) and serious infections (2% vs. 1%) was similar in patients treated with TECFIDERA or placebo, respectively (see WARNINGS AND PRECAUTIONS, Hematologic, Infections; ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Hepatic Transaminases: In placebo-controlled trials, elevations of hepatic transaminases were observed. The majority of patients with elevations had hepatic transaminases that were less than 3 times the upper limit of normal (ULN). Alanine aminotransferase (ALT) > 1 x ULN and < 3 x ULN occurred in 42% of patients treated with TECFIDERA compared to 31% of patients on placebo. Aspartate aminotransferase (AST) > 1 x ULN and < 3 x ULN occurred in 24% of patients treated with TECFIDERA compared to 19% of patients on placebo. The increased incidence of elevations of hepatic transaminases in patients treated with TECFIDERA relative to placebo was primarily seen during the first 6 months of treatment. Discontinuation of treatment due to elevated hepatic transaminases were < 1% and similar in patients treated with TECFIDERA or placebo. Elevations in transaminases ≥3 times ULN with concomitant elevations in total bilirubin >2 times ULN were not observed during placebo-controlled studies (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary, Monitoring and Laboratory Tests; ADVERSE DRUG REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Renal: Adverse events of proteinuria (proteinuria, microalbuminuria and urine albumin present) were reported at slightly higher frequencies in patients treated with TECFIDERA compared to patients that received placebo (Table 1). The overall incidence of renal and urinary adverse events, including serious adverse events and adverse events leading to discontinuation, was similar for TECFIDERA and placebo-treated patients. There were no reports of serious renal failure. On urinalysis, the percentage of patients with protein values of 1+ or greater was similar for TECFIDERA (43%) and placebo-treated patients (40%). Typically, laboratory observations of proteinuria were not progressive. Positive urine ketones occurred more frequently in patients treated with TECFIDERA than in patients who received placebo, but were not associated with increases in other renal/urinary adverse events (see ADVERSE DRUG REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Abnormal Hematologic and Clinical Chemistry Findings

Abnormal hematological and clinical chemistry findings reported in the placebo controlled multiple sclerosis clinical trials included the following:

Hematologic

- The majority of patients (> 98%) had normal lymphocyte values prior to initiating treatment. Upon

treatment with TECFIDERA, lymphocytes counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% from baseline value, but mean and median lymphocyte counts remained within normal limits. Patients with lymphocyte counts < $0.5x10^9$/L were observed in < 1% of patients treated with placebo and 6% of patients treated with TECFIDERA. In controlled and uncontrolled clinical studies, 9% of patients had lymphocyte counts ≥0.5×10^9/L and <0.8×10^9/L for at least six months. 2% of patients experienced lymphocyte counts <0.5×10^9/L for at least 6 months and in this group, the majority of lymphocyte counts remained <0.5×10^9/L with continued therapy.

- A transient increase in mean eosinophil counts was seen during the first 2 months of TECFIDERA therapy (see WARNINGS AND PRECAUTIONS, Hematologic).

Clinical Chemistry

- In the placebo-controlled studies, measurement of urinary ketones (1+ or greater) was higher in patients treated with TECFIDERA (45%) compared to placebo (10%). No untoward clinical consequences were observed in clinical trials (see ADVERSE REACTIONS, Renal).
- Levels of 1,25-dihydroxyvitamin D decreased in TECFIDERA treated patients relative to placebo (median percentage decrease from baseline at 2 years of 25% versus 15%, respectively) and levels of parathyroid hormone (PTH) increased in TECFIDERA treated patients relative to placebo (median percentage increase from baseline at 2 years of 29% versus 15%, respectively). Mean values for both parameters remained within normal range. No untoward clinical consequences were observed in clinical trials.

Less Common Clinical Trial Adverse Events (< 1%)

The following is a list of treatment-emergent adverse events reported by patients treated with TECFIDERA at any dose in MS placebo-controlled trials (n=1720) at an incidence of < 1% but at an incidence of ≥ 0.3% higher than placebo (n=836). Events that have already been included in Table 1 have been excluded. Although the events reported occurred during treatment with TECFIDERA, they were not necessarily caused by TECFIDERA.

Events are listed by system organ class in decreasing order of incidence in TECFIDERA-treated patients.

Blood and lymphatic system: eosinophilia

Cardiac disorders: supraventricular extrasystoles, atrioventricular block first degree, angina pectoris

Gastrointestinal disorders: periodontitis, dental caries, food poisoning, defaecation urgency, eructation

General disorders: non-cardiac chest pain, malaise

Hepatobiliary disorders: liver disorder

Immune system disorders: food allergy

Infections and infestations: conjunctivitis infective, cellulitis, tracheitis

Injury, poisoning and procedural complications: foot fracture, ankle fracture

Investigations: beta 2 microglobulin increased, neutrophil count decreased, blood potassium increased

Metabolism and nutrition disorders: hypercholesterolaemia

Musculoskeletal and connective tissue disorders: arthritis, joint stiffness

Neoplasms benign, malignant and unspecified: skin papilloma, lipoma

Nervous system disorders: dysgeusia, dysarthria, migraine with aura, cognitive disorder
Psychiatric disorders: mood altered

Renal and urinary disorders: urge incontinence

Reproductive system and breast disorders: breast pain

Respiratory, thoracic and mediastinal disorders: sinus congestion, asthma

Skin and subcutaneous tissue disorders: rash pruritic, skin burning sensation, rash macular, generalised erythema, rash generalised, photosensitivity reaction, rash erythematous

Vascular disorders: hyperaemia, varicose vein

Post Market Adverse Drug Reactions

During post marketing experience, hypersensitivity reactions have been reported, including rare reports of anaphylaxis and angioedema in patients treated with TECFIDERA. Signs and symptoms have included difficulty breathing, urticaria, and swelling of the throat and tongue.

Progressive multifocal leukoencephalopathy has occurred in the setting of prolonged moderate to severe lymphopenia following TECFIDERA administration (see WARNINGS AND PRECAUTIONS).

Liver function abnormalities (elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN) have been reported following TECFIDERA administration in post marketing experience. These abnormalities resolved upon treatment discontinuation.

DRUG INTERACTIONS

Overview

In humans, TECFIDERA (dimethyl fumarate) is extensively metabolized by esterases before it reaches the systemic circulation and further metabolism occurs through tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP) system. Potential drug interaction risks were not identified from *in vitro* CYP-inhibition and induction studies, a p-glycoprotein study, or studies of the protein binding of dimethyl fumarate and monomethyl fumarate (MMF, a major metabolite of dimethyl fumarate).

Drug-Drug Interactions

During treatment with TECFIDERA, simultaneous use of other fumaric acid derivatives (topical or systemic) is not recommended.

Single doses of drugs used in patients with multiple sclerosis, intramuscular interferon beta-1a and glatiramer acetate (GA), were clinically tested for potential drug-interactions with TECFIDERA and did not alter the pharmacokinetic profile of TECFIDERA. TECFIDERA is not indicated for concomitant use with these drugs.

Non-enteric coated acetylsalicylic acid 325 mg, when administered approximately 30 minutes before TECFIDERA, over 4 days of dosing in healthy adult volunteers, did not alter the pharmacokinetic profile of TECFIDERA, and reduced the occurrence and severity of flushing. Long-term use of acetylsalicylic acid is not recommended for the management of flushing. Potential risks associated with acetylsalicylic acid therapy should be considered prior to co-administration with TECFIDERA.

Interaction studies with oral contraceptives have not been performed. Based on *in vitro* CYP induction studies, an interaction with oral contraceptives is not expected. Women on oral contraceptives should be advised to also consider using non-hormonal contraceptive measures while being treated with TECFIDERA.

Pharmacodynamic interactions

Anti-neoplastic, immunosuppressive or immune modulating drugs: TECFIDERA has not been studied in patients treated with anti-neoplastic or immunosuppressive therapies and concomitant treatment is not recommended in these patients due to the potential risk of additive immune system effects. Caution should also be exercised when switching patients from long-acting therapies with immune effects to avoid additive immune system effects (see WARNINGS AND PRECAUTIONS, Hematologic).

Vaccines: The use of live attenuated vaccines may carry the risk of infection and is not recommended. Vaccines may be less effective during treatment with TECFIDERA.

Drugs associated with nephrotoxicity: The use of TECFIDERA in patients who receive chronic treatment with drugs that are associated with potential nephrotoxic risk (e.g., aminoglycosides, diuretics, NSAIDs, lithium) has not been evaluated. Therefore, caution should be exercised if TECFIDERA is used in these patients (see WARNINGS AND PRECAUTIONS, Renal; ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Corticosteroids: In the multiple sclerosis clinical trials, relapses were treated with a short course of corticosteroids. Although this was not associated with an increased rate of infection in clinical trials, patients should be reminded of the potential increased risk of infection due to additive immune system effects of corticosteroids.

Drug-Food Interactions

Food does not have a clinically significant effect on exposure of TECFIDERA. TECFIDERA may be taken with or without food.

Drug-Laboratory Interactions

Not applicable.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosing in special populations:

Renal or hepatic impairment: TECFIDERA (dimethyl fumarate) has not been studied in patients with renal or hepatic impairment. Based on the pharmacokinetics and metabolic fate of TECFIDERA in healthy adults, neither condition would be expected to affect exposure to MMF and therefore no dosage adjustment is necessary. However, caution should be exercised when treating patients with these conditions (see WARNINGS AND PRECAUTIONS, Special Populations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Pediatric patients: TECFIDERA is not indicated for use in pediatric patients (see INDICATIONS AND CLINICAL USE).

Geriatric patients: Clinical studies of TECFIDERA had limited exposure to patients aged 55 years and above, and did not include sufficient numbers of patients aged 65 and over to determine whether the safety and efficacy of TECFIDERA differs in elderly patients compared to younger patients. Based on the mechanism of action there are no theoretical reasons for any requirement for dose adjustments in the elderly. Physicians who choose to treat geriatric patients should consider that treatment with TECFIDERA in the context of a greater frequency of other concomitant diseases and concomitant drug therapy warrants caution and may necessitate additional or more frequent monitoring (see WARNINGS AND PRECAUTIONS, Special Populations).

Recommended Dose and Dosage Adjustment

Initial dose: The starting dose for TECFIDERA is 120 mg twice a day orally, for a total of 240 mg per day.

Usual dose: After 7 days, increase to the recommended dose of 240 mg twice a day orally, for a total of 480 mg per day.

Temporary dose reduction to 120 mg twice a day (total of 240 mg per day) may reduce the occurrence of flushing and gastrointestinal (GI) side effects. Within one month, the recommended dose of 240 mg twice a day orally should be resumed.

TECFIDERA can be taken with or without food. For those patients who may experience gastrointestinal side effects, taking TECFIDERA with food may improve tolerability.

Administration of 325 mg non-enteric coated acetylsalicylic acid prior to TECFIDERA dosing reduced the occurrence and severity of flushing in a 4-day healthy volunteer study. Longer term use of acetylsalicylic acid to manage flushing has not been studied and is not recommended (see ACTION AND PHARMACOLOGY).

Administration
TECFIDERA is taken orally, with or without food.

Capsules should be taken by swallowing whole. The capsule and its contents should not be crushed, divided, or dissolved, as the enteric-coating of the microtablets in the capsule helps to prevent irritant effects on the stomach.

Missed Dose
If a dose is missed, the missed dose can be taken if there is at least 4 hours between the morning and evening doses. Otherwise, treatment should be continued with the next dose as planned.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Cases of overdose with TECFIDERA have been reported. The symptoms described in these cases were consistent with the known adverse event profile of TECFIDERA. There are no known therapeutic interventions to enhance elimination of TECFIDERA nor is there a known antidote. In the event of overdose, it is recommended that symptomatic supportive treatment be initiated as clinically indicated. Safety of cumulative doses higher than 720 mg daily has not been adequately evaluated (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Dimethyl fumarate (DMF) and the metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. Dimethyl fumarate has also demonstrated anti-inflammatory effects *in vitro* and *in vivo*. The mechanism by which TECFIDERA (dimethyl fumarate) exerts therapeutic effects in multiple sclerosis is not known.

Pharmacodynamics
The primary pharmacodynamic response to TECFIDERA treatment appears to be mediated, in part, through activation of the Nrf2 pathway. Activation of the Nrf2 pathway leads to the upregulation of antioxidant response genes. Studies done *in vitro* and *in vivo* in animals suggest that the Nrf2 dependent upregulation of antioxidant response genes by DMF and/or MMF can protect various types of cells and tissues, including some from the CNS, from experimental toxic oxidative stress.

Dimethyl fumarate has demonstrated anti-inflammatory effects *in vitro*, with a reduction in pro-inflammatory cytokine and chemokine production that was stimulated by activation of the TLR-4 pathway via LPS administration. Additionally, a mechanistic role for dimethyl fumarate has been identified in inducing type II dendritic cells and biasing immune cell differentiation towards an anti-inflammatory T_H2 phenotype. These anti-inflammatory responses are thought to reduce aberrant

immune cell activation, which occurs in auto-immune diseases such as MS. These anti-inflammatory effects observed *in vitro* were consistent with *in vivo* studies. In the Phase 3 clinical trials mean lymphocyte counts decreased by approximately 30% from baseline values during the first year and remained stable at the reduced level.

An analysis over a 4-day dosing period, in healthy adult volunteers, indicated that flushing scores decreased from a maximum on the first day of dosing, despite higher plasma MMF concentrations at the final dose. Administration of non-enteric coated acetylsalicylic acid 325 mg, 30 minutes prior to dosing, attenuated flushing (see DOSAGE AND ADMINISTRATION).

Effect on Cardiovascular System: Single doses of 240 mg or 360 mg TECFIDERA did not have any effect on the QTc interval when compared to placebo in a specialized QTc study in healthy subjects.

Pharmacokinetics

Orally administered TECFIDERA undergoes rapid presystemic hydrolysis by esterases and is converted to its primary metabolite, monomethyl fumarate (MMF), which is also active. 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: TECFIDERA concentration-time profiles are characterized by high inter-individual variability. The T_{max} of TECFIDERA is 2-5 hours. As TECFIDERA microtablets are protected by an enteric coating, absorption does not commence until the microtablets leave the stomach (generally less than 1 hour post-dose). Following 240 mg administered twice a day with food, the median peak (C_{max}) was 1.72 mg/L and overall (AUC) exposure was 8.02 h.mg/L in subjects with MS (C_{max} and AUC increased approximately dose proportionally in the dose range studied (120 mg to 360 mg).

Food does not have a clinically significant effect on exposure of TECFIDERA. Therefore, TECFIDERA may be taken with or without food.

Based on the results of ANOVA, body weight is the main covariate of exposure (by C_{max} and AUC) in relapsing remitting multiple sclerosis (RRMS) subjects, but did not affect safety and efficacy measures evaluated in the clinical studies. Gender and age did not have a statistically significant impact on C_{max} and AUC.

Distribution: The apparent volume of distribution following oral administration of 240 mg TECFIDERA varies between 53 and 73 L in healthy subjects. Human plasma protein binding of MMF generally ranges between 27% - 40%.

Metabolism: In humans, TECFIDERA is extensively metabolized by esterases, which are ubiquitous in the gastrointestinal tract, blood and tissues, before it reaches the systemic circulation. Further metabolism occurs through the tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP) system. A single 240 mg ^{14}C-dimethyl fumarate dose study identified monomethyl fumarate, fumaric and citric acid, and glucose as the major metabolites in plasma. The downstream metabolism of fumaric and citric acid occurs through the TCA cycle, with exhalation of CO_2 serving as a primary route of elimination. Less than 0.1% of the dose is excreted as unchanged dimethyl fumarate in urine.

Potential drug interaction risks were not identified for monomethyl fumarate from *in vitro* CYP-inhibition and induction studies, a p-glycoprotein study, or protein binding studies.

Excretion: Exhalation of CO_2 is the primary route of TECFIDERA elimination accounting for approximately 60% of the dose. Renal and fecal elimination are secondary routes of elimination, accounting for 15.5% and 0.9% of the dose respectively.

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

Linearity: TECFIDERA exposure increases in an approximately dose proportional manner with single and multiple doses in the 120 to 360 mg dose range studied.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of TECFIDERA in patients younger than 18 years of age have not been evaluated. TECFIDERA is not indicated in patients below the age of 18.

Geriatrics: The pharmacokinetics in patients aged 65 and over has not been studied (see WARNINGS AND PRECAUTIONS, Special Populations – Geriatrics).

Body Weight & Gender: Body weight is the main covariate of exposure (by C_{max} and AUC) in relapsing remitting multiple sclerosis (RRMS) subjects, but did not affect safety and efficacy measures evaluated in the clinical studies. Gender and age did not have a statistically significant impact on $C_{max.}$

Race: Race and ethnicity have no effect on the pharmacokinetics of TECFIDERA.

Hepatic Insufficiency: As dimethyl fumarate and MMF are metabolized by esterases present in most tissues, without the involvement of the CYP450 system, evaluation of pharmacokinetics in individuals with hepatic impairment was not conducted (see WARNINGS AND PRECAUTIONS, Special Populations – Hepatic Impairment).

Renal Insufficiency: Since the renal pathway is a secondary route of elimination for TECFIDERA accounting for less than 16% of the dose administered, evaluation of pharmacokinetics in individuals with renal impairment was not conducted (see WARNINGS AND PRECAUTIONS, Special Populations – Renal Impairment).

STORAGE AND STABILITY

Store TECFIDERA (dimethyl fumarate) capsules between 15 and 30°C in the original packaging in order to protect from light.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TECFIDERA is available as enteric-coated microtablets in a hard gelatin capsule containing 120 mg or 240 mg of dimethyl fumarate.

120 mg Capsules: Have a green cap and white body and are printed with "BG-12 120 mg" in black ink.

120 mg Packaging:

14 Capsule Cartons: one folded wallet containing 14 capsules per blister
56 Capsule Cartons: two folded wallets containing two blisters with 14 capsules per blister

The capsules are in a PVC/PE/PVDC aluminum blister sealed inside a folded wallet.

240 mg Capsules: Have a green cap and body and are printed with "BG-12 240 mg" in black ink.

240 mg Packaging:

56 Capsule Cartons: two folded wallets containing two blisters with 14 capsules per blister

The capsules are in a PVC/PE/PVDC aluminum blister sealed inside a folded wallet.
120 mg non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, methacrylic acid copolymer (type A), methacrylic acid copolymer dispersion, microcrystalline cellulose, polysorbate 80, simethicone, sodium lauryl sulfate, talc and triethyl citrate. The capsule shell contains black iron oxide, FD&C Blue 1, gelatin, titanium dioxide and yellow iron oxide.

240 mg non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, methacrylic acid copolymer (type A), methacrylic acid copolymer dispersion, polysorbate 80, silicified microcrystalline cellulose, simethicone, sodium lauryl sulfate, talc and triethyl citrate. The capsule shell contains black iron oxide, FD&C Blue 1, gelatin, titanium dioxide and yellow iron oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

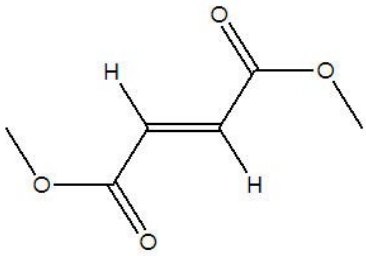
Proper name: Dimethyl fumarate

Chemical name: Dimethyl (E)-butenedioate

CAS: 624-49-7

Molecular formula and molecular mass: $C_6H_8O_4$, molecular mass 144.13

Structural formula:



Physicochemical properties: Dimethyl fumarate is a white to off-white powder that is highly soluble in water.

CLINICAL TRIALS

Study demographics and trial design

Table 2- Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 1 (DEFINE)	Randomized, double-blind, placebo-controlled study.	TECFIDERA 240 mg twice or three times daily, or placebo, (oral). 2 year study.	TECFIDERA BID: n=410 TECFIDERA TID: n=416 Placebo: n=408	39 (18 – 56)	Male: 26% Female: 74%
Study 2 (CONFIRM)	Multicenter, randomized, double-blind, placebo controlled study with a rater-blinded reference comparator of glatiramer acetate (GA).	TECFIDERA 240 mg twice or three times daily or placebo (oral), or GA. 2 year study.	TECFIDERA BID: n=359 TECFIDERA TID: n=345 Placebo: n=363 GA: n=350	37 (18 – 56)	Male: 30% Female: 70%

The efficacy and safety of TECFIDERA (dimethyl fumarate) was demonstrated in two studies 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 either 240 mg twice or three times a day. Both studies included patients with Expanded Disability Status Scale (EDSS) scores ranging from 0 to 5, who had experienced at least 1 relapse during the year prior to randomization, or, within 6 weeks of randomization had a brain Magnetic Resonance Imaging (MRI) demonstrating at least one gadolinium+ (Gd+) lesion.

Study 1 (DEFINE): Study 1 was a 2-year randomized, double-blind, placebo-controlled study in 1234 patients with RRMS who had not received interferon-beta or glatiramer acetate (GA) for at least the previous 3 months or natalizumab for at least the previous 6 months. Neurological evaluations were performed at baseline, every 3 months and at time of suspected relapse. MRI evaluations were performed at baseline, month 6, and year 1 and 2. The primary endpoint in Study 1 was the reduction in the proportion of patients relapsed at 2 years.

Patients were randomized to receive TECFIDERA 240 mg twice a day (n=410), TECFIDERA 240 mg three times a day (n=416), or placebo (n=408) for up to 2 years (96 weeks). Median age: 39 years, median years since diagnosis: 4.0 years and median EDSS score at baseline: 2.0. Mean time on study was 84 weeks on 240 mg twice a day, 83 weeks on 240 mg three times a day and 85 weeks on placebo.

The proportion of patients relapsed at 2 years was significantly lower ($p < 0.0001$) in the group treated with TECFIDERA than in the group that received placebo (Table 3, Figure 1).

Clinical secondary endpoints included annualized relapse rate (ARR), and time to 12-week confirmed disability progression at 2 years. 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. The annualized relapse rate and time to 12-week confirmed disability progression were reduced in patients treated with TECFIDERA compared to placebo (Table 3).

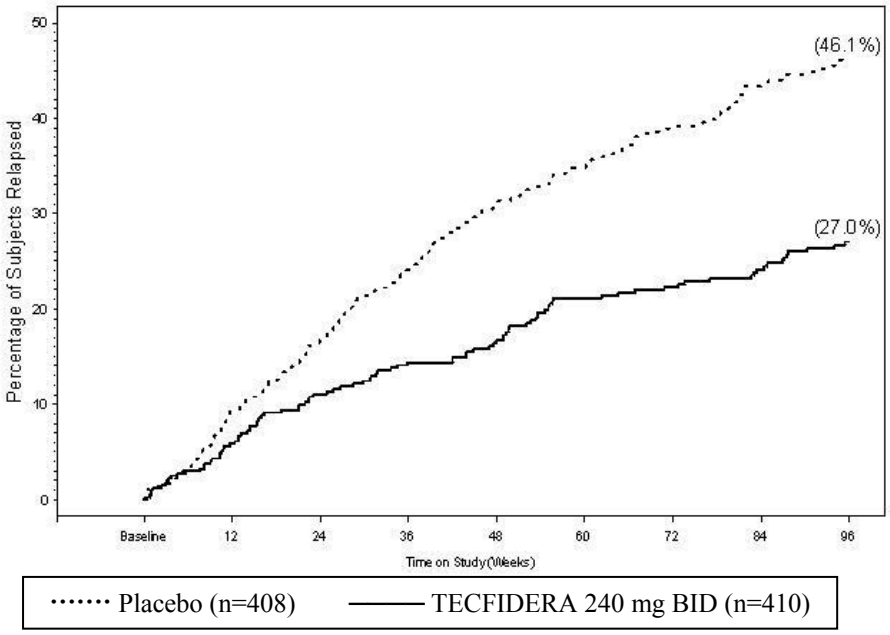
Secondary MRI endpoints included the number of new or newly enlarging T2 hyperintense lesions and number of Gd-enhancing lesions over 2 years, and both were reduced in patients treated with TECFIDERA compared to patients who received placebo (Table 3).

The 240 mg three times daily dose resulted in no additional benefit over the TECFIDERA 240 mg twice daily dose.

Table 3 – Study 1 (DEFINE) Study Results

	TECFIDERA, 240 mg BID (N=410)	**Placebo (N=408)**
Primary Endpoint		
Proportion relapsing at 2 years Relative risk reduction (percentage)	0.270 49%	0.461
Secondary Endpoints		
Annualized relapse rate Relative risk reduction (percentage)	0.172 53%	0.364
Proportion with disability progression Relative risk reduction (percentage)	0.164 38%	0.271
Mean number of new or newly enlarging T2 lesions over 2 years Relative reduction (percentage)	2.6 85%	17.0
Mean number of Gd lesions at 2 years (median) Relative odds reduction (percentage)	0.1 (0) 90%	1.8 (0)

Figure 1 - Time to First Relapse in Study 1 (DEFINE) – Percentage of Patients Relapsed at 2 years



NOTE 1: Only relapses confirmed by the INEC (Independent Neurology Evaluation Committee) were included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study were censored at the time of switch/withdrawal.

Study 2 (CONFIRM): Study 2 was a 2-year, randomized, double-blind, placebo-controlled study in 1417 patients with RRMS. Study 2 included an open label reference comparator group that received glatiramer acetate (GA). Patients included in the study had not received interferon-beta for at least the previous 3 months, natalizumab for at least the previous 6 months or glatiramer acetate at any time previously. The efficacy and safety evaluations were identical to Study 1 and the endpoints were consistent between the studies. The primary endpoint in Study 2 was the annualized relapse rate at 2 years.

Patients were randomized to receive TECFIDERA 240 mg twice a day (n=359), TECFIDERA 240 mg three times a day (n=345), placebo (n=363) or glatiramer acetate (n=350) for up to 2 years (96 weeks). Median age: 37 years, median years since diagnosis: 3.0 years and median EDSS score at baseline: 2.5. Mean time on study was 84 weeks on TECFIDERA, 86 weeks on placebo and 88 weeks on glatiramer acetate.

The annualized relapse rate at 2 years, was significantly lower in patients treated with TECFIDERA than in patients treated with placebo (0.224 for TECFIDERA vs. 0.401 for placebo, $p < 0.0001$), corresponding to a 44% relative reduction.

Clinical secondary endpoints included the proportion of patients relapsed at 2 years, and time to 12-week confirmed disability progression at 2 years (defined as in Study 1). The proportion of patients relapsed at 2 years was reduced in the TECFIDERA group compared to the placebo group. Time to 12-week confirmed disability progression was not significantly reduced for patients on TECFIDERA compared to those on placebo (Table 4).
Secondary MRI endpoints included the number of new or newly enlarging T2 hyperintense lesions and number new of T1 hypointense lesions at 2 years, and both were reduced in patients treated with TECFIDERA compared to those on placebo (Table 4).

Table 4 - Study 2 (CONFIRM) Study Results

	TECFIDERA, 240 mg BID (N=359)	**Placebo (N=363)**
Primary Endpoint		
Annualized relapse rate Relative risk reduction (percentage)	0.224 44%	0.401
Secondary Endpoints		
Proportion relapsing at 2 years Relative risk reduction (percentage)	0.291 34%	0.410
Proportion with disability progression Relative risk reduction (percentage)	0.128 21%	0.169
Mean number of new or newly enlarging T2 lesions over 2 years Relative reduction (percentage)	5.1 71%	17.4
Mean number of new T1 hypointense lesions over 2 years Relative reduction (percentage)	3.0 57%	7.0

DETAILED PHARMACOLOGY

Mechanism of Action

Preclinical studies indicate that dimethyl fumarate pharmacodynamic responses appear to be mediated, in part, through activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, which is the primary cellular defense system for responding to a variety of potentially toxic stimuli, including inflammatory and oxidative stress, through up-regulation of antioxidant response genes. In studies done *in vitro* and *in vivo* in animals DMF and/or MMF treatment reduced inflammatory responses in both peripheral and central cells, and central nervous system cells were protected against experimentally-induced toxic oxidative insults when treated with DMF. The mechanism by which TECFIDERA exerts therapeutic effects in multiple sclerosis is not known.

Pharmacodynamic Effects

Activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) Pathway: The TECFIDERA mechanism of action appears to be mediated, at least in part, through activation of the Nrf2 anti-oxidant response pathway.

Effects on Immune System: In preclinical studies, TECFIDERA demonstrates anti-inflammatory and immunomodulatory properties. Dimethyl fumarate and MMF significantly reduce immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli. In addition, lymphocytes show down-regulation of pro-inflammatory cytokine profiles (T_H1, T_H17), and are biased towards anti-inflammatory production (T_H2). Dimethyl fumarate also demonstrates efficacy in models of inflammatory and neuroinflammatory injury, and also appears to promote improvement in blood brain barrier integrity.

Effects on Central Nervous System: Dimethyl fumarate and MMF significantly improved cell viability after oxidative challenge in primary cultures of astrocytes and neurons. In preclinical studies MMF was able to penetrate into the central nervous system. Acute neurotoxic injury models and genetic models of neurodegenerative disease (experimental autoimmune encephalitis) have demonstrated that dimethyl fumarate is effective in reducing neuronal and functional damage resulting from various types of experimental toxic stimuli and other forms of cellular stress inherent in animal models of neurodegenerative disease states.

Safety Pharmacology

Non-clinical safety pharmacology studies in mice and dogs indicate that dimethyl fumarate and MMF do not have any drug-related adverse effects on the CNS, respiratory and cardiovascular systems. DMF and MMF revealed no relevant interaction at hERG channels and did not alter cardiac conduction of canine Purkinje fibers or the ECG in a cardiovascular dog study. This is in agreement with the absence of any ECG effect in the chronic toxicity studies with DMF in dogs and monkeys.

Non-Clinical Pharmacokinetics

Pharmacokinetic studies of dimethyl fumarate and its primary active metabolite monomethyl fumarate (MMF) have been conducted in mice, rats, dogs and monkeys, as well as pregnant rats and rabbits. In all *in vivo* preclinical studies, except the dog regional absorption study, dimethyl fumarate was administered via the oral route. Regional absorption was determined in male dogs given a single dose of dimethyl fumarate directly to sites within the duodenum, jejunum, ileum and colon, and

demonstrated that absorption can occur throughout the intestine, but the majority occurred in the duodenum and jejunum. Dimethyl fumarate concentrations were below the LLOQ at all-time points in all animal species after oral administration, as dimethyl fumarate is rapidly pre-systemically hydrolyzed to MMF after oral administration and therefore PK analysis was only performed on MMF. Overall, the absorption, distribution, metabolism and excretion of dimethyl fumarate are similar across all species examined including humans.

The absorption of dimethyl fumarate was rapid, yielding T_{max} values between 10-30 min after oral dosing. The elimination was also rapid, characterized by terminal phase half-lives of less than 1 hour in both rats and dogs. The overall exposure (AUC and C_{max}) increased in all species with dose, generally in a dose proportional manner. Maximum tissue concentrations in rats, with the exception of the gastro-intestinal (GI) tract, were observed in organs of excretion, glandular tissues, and brain. Gender difference in pharmacokinetics has been detected in the rat only with the female exposure up to two times higher than the male. Plasma protein binding of MMF was low in rat, dog, monkey, and human plasma (unbound 55 to 100%) and binding was concentration independent.

Glucose is the predominant circulating metabolite in male and female rats, accounting for 50% of the plasma total extractable radioactivity. Other major metabolites, fumaric acid and citric acid combined, accounted for 33% of the circulating radioactivity. The total concentrations of fumaric acid after dimethyl fumarate administration in rats and dogs remained within the physiological limits at all measurement times. MMF accounted for less than 0.2% of the total circulating radioactivity $AUC_{(0\text{-}72h)}$ in rat plasma. There were no apparent gender related differences in the metabolic profiles. All of the metabolites identified in humans were found in the rat.

Total recovery of the administered radioactive dose was greater than 89% in both male and female rats. The primary route of elimination of dimethyl fumarate is exhalation of CO_2 followed by urine. The majority of dose was recovered in the expired air (~63%), as a result of dimethyl fumarate being converted to CO_2 as an end metabolite via the tricarboxylic acid (TCA) cycle. Cysteine and/or N-acetyl cysteine conjugates of mono- and di-methyl succinate were the major urinary metabolites in rat urine. Less than 0.2% of the dose was excreted in urine as unchanged dimethyl fumarate.

TOXICOLOGY

All nonclinical safety studies in rodents and non-rodents were conducted with a dimethyl fumarate suspension (in 0.8% hydroxypropyl methylcellulose) administered by oral gavage, except acute and chronic studies in the dog that were conducted with oral administration of the TECFIDERA(dimethyl fumarate) capsule.

Kidney changes were observed after repeated oral administration of dimethyl fumarate in mice, rats, dogs, and monkeys. Renal tubule epithelial regeneration, suggestive of tubule epithelial injury, was observed in all species. Exacerbation of age-related nephropathy and renal tubular hyperplasia were observed in mice and rats with chronic and life time dosing (2 year study) at all dose levels; hence there are no safety margins. In dogs, renal tubular dilatation and hypertrophy and hyperplasia of papillary urothelium at all dose levels, and tubular epithelial regeneration at higher dose levels indicate no safety margin was identified for renal toxicity. In monkeys, single cell necrosis and regeneration of tubular epithelial cells and, interstitial fibrosis with tubular atrophy were observed. The findings in

monkeys were observed after daily oral doses of dimethyl fumarate for 12 months at approximately 2 times the RHD for single cell necrosis and at 6 times the RHD for interstitial fibrosis, based on AUC. The relevance of these findings to human risk is not known.

Parathyroid hyperplasia and adenoma in the 2-year rat study were considered secondary to renal toxicity.

In the testes, degeneration of the seminiferous epithelium was seen in rats and dogs at the high dose in an 11-month study and interstitial (Leydig) cell hyperplasia was seen in rats at all dose levels in a male fertility study and with lifetime dosing (2-year study). Findings were observed at less than the RHD in rats, and 3 times the RHD in dogs (AUC basis). The relevance of these findings to humans is not known.

In the forestomach (nonglandular stomach) of mice and rats, squamous epithelial hyperplasia and hyperkeratosis, inflammation, squamous cell papilloma and carcinoma were observed in studies of at least 3 months duration. The forestomach of mice and rats does not have a human counterpart.

Findings in the liver in a 6-month study in rats were reported only in rats and not in mice, dogs or monkeys. Findings in the retina in the mouse carcinogenicity study were reported only in this study and not with other species.

Carcinogenisis: Carcinogenicity studies of dimethyl fumarate were conducted in mice and rats. In mice, dimethyl fumarate was administered at oral doses of 25, 75, 200, and 400 (dose reduced from 600) mg/kg/day for up to 2 years. The incidence of renal tubular adenoma (benign) and carcinoma was increased at 4 times the RHD on an AUC basis. Renal tumours were considered to be the result of the exacerbation of nephropathy caused by chronic renal toxicity. The relevance of these findings to human risk is unknown. The incidence of leiomyosarcoma, papilloma, and squamous cell carcinoma in the nonglandular stomach (forestomach) was increased at 4 times the RHD (AUC basis). The forestomach of mice does not have a human counterpart. Plasma MMF exposure (AUC) at the highest dose that was not associated with tumors in mouse (75 mg/kg/day) was similar to that in humans at the RHD of 480 mg/day.

In rats, dimethyl fumarate was administered at oral doses of 25, 50, 100 and 150 mg/kg/day for up to 2 years. In males, an increase in the incidence of benign interstitial cell (Leydig cell) adenoma of the testes was observed at 1.5 times the RHD based on relative AUC values. The incidence of squamous cell papilloma and carcinoma of the nonglandular stomach (forestomach) was increased below the RHD. The forestomach of rats does not have a human counterpart. Plasma MMF AUC at the lowest dose tested was lower than that in humans at the RHD.

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

Fertility: Administration of dimethyl fumarate to male rats at daily oral doses of 75, 250, and 375 mg/kg prior to and during mating had no effects on male fertility up to the highest dose tested (9 times the RHD based on mg/m^2). Administration of dimethyl fumarate to female rats at daily oral doses of

25, 100, 250 mg/kg/day prior to and during mating, and continuing to Day 7 gestation, caused disruption of the estrous cycle and increases in embryolethality at the highest dose tested. The highest dose not associated with adverse effects (100 mg/kg/day) is twice the RHD on a mg/m^2 basis. Testicular toxicity (germinal epithelial degeneration, atrophy, hypospermia, and/or hyperplasia) was observed at clinically relevant doses in mouse, rat, and dog in subchronic and chronic oral toxicity studies of DMF.

Teratogenicity: No malformations were observed at any dose of dimethyl fumarate in rats or rabbits. Administration of dimethyl fumarate at daily oral doses of 25, 100, and 250 mg/kg/day to pregnant rats during the period of organogenesis resulted in reductions in maternal body weight at 4 times the RHD on an AUC basis, and reductions in fetal weight, increased alterations and reduced ossification (metatarsals and hindlimb phalanges) at 11 times the RHD on an AUC basis. The effects on the fetus may have been secondary to maternal toxicity.

Administration of dimethyl fumarate at daily oral doses of 25, 75, and 150 mg/kg/day to pregnant rabbits during organogenesis had no effect on embryo-fetal development and resulted in reductions in maternal body weight at doses 7 times the RHD and increased abortion at 16 times the RHD on an AUC basis.

Administration of dimethyl fumarate at daily oral doses of 25, 100, and 250 mg/kg/day to rats during pregnancy and lactation resulted in lower body weights in the F1 offspring, and delays in sexual maturation in F1 males at 11 times the RHD on an AUC basis. There were no effects on fertility in the F1 offspring. The effects on the F1 offspring may have been secondary to maternal toxicity.

REFERENCES

1. Bruck W, Bitsch A, Kolenda H, et al. Inflammatory central nervous system demyelination: correlation of magnetic resonance imaging findings with lesion pathology. Ann Neurol. 1997; 42(5): 783-93.

2. Fox RJ, Miller DH, Philips T, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012; 367: 1087-97.

3. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012; 367: 1098-107.

4. Ghoreschi, K., J. Bruck, Kellerer C, et al. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. J Exp Med. 2011; 208(11): 2291-303.

5. Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008; 372(9648): 1463-72.

6. Kappos L, Gold R, Miller DH, et al. Effect of BG-12 on contrast-enhancing lesions in patients with relapsing-remitting multiple sclerosis: subgroup analyses from the phase 2b study. Mult Scler. 2012; 18(3): 314-21.

7. Kobayashi, M., L. Li, et al. The antioxidant defense system Keap1-Nrf2 comprises a multiple sensing mechanism for responding to a wide range of chemical compounds. Mol Cell Biol 2009; 29(2): 493-502.

8. Linker RA, Lee DH, Ryan S, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain. 2011; 134(Pt 3): 678-92.

9. Wilms, H., J. Sievers, et al. Dimethyl fumarate inhibits microglial and astrocytic inflammation by suppressing the synthesis of nitric oxide, IL-1beta, TNF-alpha and IL-6 in an *in-vitro* model of brain inflammation. J Neuroinflammation. 2010; 7: 30.

10. Zhao J, Moore AN, Redell JB, et al. Enhancing expression of Nrf2-driven genes protects the blood brain barrier after brain injury. J Neurosci. 2007; 27(38): 10240-8.

PART III: CONSUMER INFORMATION

TECFIDERA®
Dimethyl fumarate

This leaflet is part III of a three-part "Product Monograph" published when TECFIDERA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TECFIDERA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TECFIDERA is a prescription medication to treat relapsing remitting multiple sclerosis (MS). TECFIDERA does not cure MS, but helps to reduce the number of flare-ups (relapses) that occur and slow the build-up of physical problems due to MS (disability progression).

What it does:
TECFIDERA may work by changing the way the body's immune system works, to help keep it from further damaging your brain and spinal cord.

When it should not be used:
Do not take TECFIDERA if you:
Have an allergy or are sensitive to dimethyl fumarate or any ingredients in this medicine.

TECFIDERA should not be used in children and adolescents under 18 years, because it has not been studied in MS patients younger than 18 years of age.

What the medicinal ingredient is:
Dimethyl fumarate.

What the nonmedicinal ingredients are:
Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, methacrylic acid copolymer (type A), methacrylic acid copolymer dispersion, microcrystalline cellulose, polysorbate 80, silicified microcrystalline cellulose, simethicone, sodium lauryl sulfate, talc, and triethyl citrate.

The capsule shell contains black iron oxide, FD&C Blue 1, gelatin, titanium dioxide, and yellow iron oxide.

What dosage forms it comes in:
Delayed-release capsules: 120 mg and 240 mg

WARNINGS AND PRECAUTIONS

BEFORE you use TECFIDERA talk to your doctor or pharmacist if:

- You have or have had low white blood cell counts (low lymphocytes). Low lymphocyte counts may be caused by another illness that affects the immune system (for example, immunodeficiency syndrome), bone marrow transplantation, or other treatments that can suppress the immune system.
- You have an infection.
- You have liver or kidney disease.
- You have a disease of the stomach or bowel.
- You are pregnant or planning to become pregnant.
- You are breast-feeding.

INTERACTIONS WITH THIS MEDICATION

You should tell your doctor(s) if you are taking any other prescription or non-prescription medicines. This includes any vitamin or mineral supplements, or herbal products.

- **Fumaric acid.** Do not use TECFIDERA with other types of fumaric acid. Ask your doctor or pharmacist if you are not sure what other products may contain fumaric acids.
- **Medicines that affect the immune system** including some commonly used cancer treatments and other medicines used to treat MS, such as, natalizumab, fingolimod, or mitoxantrone. TECFIDERA should not be started while you are on other MS medications. If you stop taking one of these medicines to switch to TECFIDERA you may be required to wait before starting TECFIDERA. The amount of time you may need to wait will vary, depending on the treatment. Your doctor will know how long you may need to wait.
- **Medicines that can affect the kidneys**, such as antibiotics from the aminoglycoside class, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, or lithium. TECFIDERA has not been studied in patients who take these drugs regularly.
- **Vaccines.** During treatment with TECFIDERA, administration of vaccines containing live virus is not recommended.
- **Oral contraceptives.** TECFIDERA may make oral contraceptives less effective. Consider using an extra form of contraception while you are taking TECFIDERA.

PROPER USE OF THIS MEDICATION

Always follow your doctor's instructions for taking TECFIDERA. You should check with your doctor or pharmacist if you are not sure.

Swallow whole. Do not divide, crush, dissolve, suck, or chew the capsule.

TECFIDERA can be taken with or without food.

TECFIDERA capsules are packaged in a folding blister card inside a carton. Remove the capsules from the blister by pushing them through the foil.

Your doctor may reduce your dose if you have certain side effects. Do not reduce your dose unless your doctor tells you to

Usual adult dose:

Starting dose: one 120 mg capsule twice a day (one in the morning and one in the evening).
Starting total daily dose: 240 mg a day.

Take this starting dose for the first 7 days, and then take the regular dose.

Regular dose: one 240 mg capsule twice a day (one in the morning and one in the evening).
Regular total daily dose: 480 mg a day.

Overdose:

If you have taken more TECFIDERA than your doctor has recommended, contact a regional Poison Control Centre immediately and a health care practitioner, or go the nearest hospital emergency department even if there are no symptoms. Take the medication package with you when you go to the hospital.

Missed Dose:
If you forget or miss a dose, do not double your next dose.

You may take the missed dose if you leave at least 4 hours between the morning and evening doses, otherwise wait and take your next dose as planned.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
Flushing and stomach upset. People are more likely to have these side effects when they first start taking TECFIDERA (mostly during the first month). Most people have mild to moderate symptoms and they tend to go away over time.

If you become flushed **and** get swelling of the face, lips, mouth or tongue, wheezing, difficulty breathing or shortness of breath, **stop taking TECFIDERA and seek emergency medical assistance.**

Signs of stomach upset may include:
- Diarrhea
- Nausea (feeling like you are going to be sick)
- Stomach pain or stomach cramps
- Vomiting (throwing up)
- Indigestion

Talk to your doctor about how to manage these side effects. Your doctor may reduce your dose. Do not reduce your dose unless your doctor tells you to.

Taking TECFIDERA with food may help manage these side effects. Your doctor may recommend taking an over-the-counter pain and fever reducer, such as aspirin, for a few days to manage signs of flushing.

TECFIDERA can cause abnormal blood and urine test results, including decreases in your white blood cell count. Your doctor will decide when to perform blood and urine tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Common	**Flushing** (symptoms of severe flushing may include general swelling, rash, itchiness)	✓		
	Gastrointestinal (GI) events (symptoms include diarrhea, nausea, stomach pain, vomiting, indigestion)	✓		
	Low levels of white blood cells (lymphocytes) (symptoms may include serious infections, e.g. pneumonia, or being more prone to infections)		✓	
	Proteins (albumin) in urine (symptoms may include swelling of the face or legs)		✓	
	Increased levels of liver enzymes (ALT, AST) in the blood (symptoms may include loss of appetite, fatigue, yellowing of the skin or eyes, or dark urine)		✓	
Un-common	**Allergic reaction** (symptoms include rash, itching, difficulty breathing, swelling of the face, lips, tongue or throat)			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Rare	**Progressive multifocal leukoencephal-opathy (PML), a rare brain infection.** (symptoms may include: progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, changes in thinking, memory and orientation, confusion, personality changes)			✓

This is not a complete list of side effects. For any unexpected effects while taking TECFIDERA, contact your doctor or pharmacist.

HOW TO STORE IT

Store TECFIDERA at room temperature (between 15 to 30°C). Protect TECFIDERA from light. Store the capsules in their original packaging. Do not take your medicine after the expiry date shown on the carton. Keep out of reach and sight of children.

Medicines should not be disposed of in waste water or household garbage. Ask your pharmacist how to dispose of medicines you no longer need.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Biogen Canada Inc., at: 1-855-MSONE-00 (1-855-676-6300)

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