PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] Sandoz Dimethyl Fumarate Delayed-Release Capsules

Dimethyl Fumarate Delayed-Release Capsules

delayed-release capsules, 120 mg and 240 mg, oral

Antineoplastic and Immunomodulating Agents

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Date of Initial Authorization:
OCT 4, 2021

Date of Revision:
SEP 14, 2022

Submission Control Number: 266762

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	09/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sandoz Dimethyl Fumarate Delayed-Release Capsules (dimethyl fumarate delayed-release capsules) is indicated as monotherapy for:

- treatment of relapsing remitting multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the progression of disability.

The efficacy of dimethyl fumarate delayed-release capsules in patients with primary progressive multiple sclerosis has not been established.

Sandoz Dimethyl Fumarate Delayed-Release Capsules should only be prescribed by clinicians who are experienced in the diagnosis and management of multiple sclerosis.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of dimethyl fumarate delayed-release capsules in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of dimethyl fumarate delayed-release capsules did not include sufficient numbers of patients aged 65 and over to determine whether the safety and efficacy of dimethyl fumarate delayed-release capsules may differ in elderly patients compared to younger patients. Physicians who choose to treat geriatric patients should consider that treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules 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 7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Sandoz Dimethyl Fumarate Delayed-Release Capsules is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredients, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Dosing in special populations:

- *Renal or hepatic impairment:* Dimethyl fumarate delayed-release capsules have not been studied in patients with renal or hepatic impairment. Based on the pharmacokinetics and metabolic fate of dimethyl fumarate delayed-release capsules 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 7 WARNINGS AND PRECAUTIONS, Special Populations; 10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

- *Pediatric patients:* Sandoz Dimethyl Fumarate Delayed-Release Capsules is not indicated for use in pediatric patients (see 1 INDICATIONS).

- *Geriatric patients:* Clinical studies of dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules 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 Sandoz Dimethyl Fumarate Delayed-Release Capsules 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 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

4.2 Recommended Dose and Dosage Adjustment

- **Initial dose:** The starting dose for Sandoz Dimethyl Fumarate Delayed-Release Capsules 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.

Sandoz Dimethyl Fumarate Delayed-Release Capsules can be taken with or without food. For those patients who may experience gastrointestinal side effects, taking Sandoz Dimethyl Fumarate Delayed-Release Capsules with food may improve tolerability.

Administration of 325 mg non-enteric coated acetylsalicylic acid prior to dimethyl fumarate

delayed-release capsules 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 10 CLINICAL PHARMACOLOGY).

4.4 Administration

Sandoz Dimethyl Fumarate Delayed-Release Capsules 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.

4.5 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.

5 OVERDOSAGE

Cases of overdose with dimethyl fumarate delayed-release capsules have been reported. The symptoms described in these cases were consistent with the known adverse event profile of dimethyl fumarate delayed-release capsules. There are no known therapeutic interventions to enhance elimination of dimethyl fumarate delayed-release capsules 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 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Delayed-release capsules / 120 mg and 240 mg	Colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, methacrylic acid copolymer, methacrylic acid - methyl methacrylate copolymer (1:1), silicified microcrystalline cellulose, talc, and triethyl citrate. The capsule shell contains FD&C blue 1, gelatin, iron oxide black, iron oxide yellow, propylene glycol, shellac, and titanium dioxide.

Sandoz Dimethyl Fumarate Delayed-Release Capsules is available as enteric-coated microtablets in a hard gelatin capsule containing 120 mg or 240 mg of dimethyl fumarate.

120 mg Capsules
Size "0" hard gelatin capsules with green cap and white body, printed with "HR1" in black ink on capsule body containing White to off-white, round, biconvex enteric coated tablets plain on both the sides.

120 mg Packaging:
14's count HDPE pack
500's count HDPE pack

14 Capsule Cartons: One blister containing 14 capsules
56 Capsule Cartons: Four blisters with 14 capsules per blister

240 mg Capsules
Size "0" hard gelatin capsules with green cap and body, printed with "HR2" in black ink on capsule body containing White to off-white, round, biconvex enteric coated tablets plain on both the sides.

240 mg Packaging
46's count HDPE pack
60's count HDPE pack
180's count HDPE pack
500's count HDPE pack

56 Capsule Cartons: Four blisters with 14 capsules per blister

7 WARNINGS AND PRECAUTIONS

General
During treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules, simultaneous use of other fumaric acid derivatives (topical or systemic) is not recommended.

Gastrointestinal
Sandoz Dimethyl Fumarate Delayed-Release Capsules may cause gastrointestinal adverse events. In placebo controlled clinical trials in patients with multiple sclerosis, 48% of patients treated with dimethyl fumarate delayed-release capsules compared to 36% of patients that received placebo, experienced gastrointestinal adverse events. The increased frequency of gastrointestinal adverse events with dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules than in patients who received placebo (see 8

ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions).

Administration of Sandoz Dimethyl Fumarate Delayed-Release Capsules with food or a temporary dose reduction to 240 mg/day may improve tolerability in patients who experience gastrointestinal adverse events (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

Dimethyl fumarate delayed-release capsules have not been evaluated in patients with severe active gastrointestinal disease and caution should be exercised when treating these patients.

Hematologic

Sandoz Dimethyl Fumarate Delayed-Release Capsules (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 dimethyl fumarate delayed-release capsules then remained stable at this reduced level for the duration of treatment. Six percent (6%) of dimethyl fumarate delayed-release capsule patients and < 1% of placebo patients experienced lymphocyte counts $<0.5x10^9/L$ (lower limit of normal $0.91x10^9/L$). 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 dimethyl fumarate delayed-release capsules, 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 Sandoz Dimethyl Fumarate Delayed-Release Capsules, 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 Sandoz Dimethyl Fumarate Delayed-Release Capsules 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.
- In patients with lymphocyte counts below lower limit of normal (LLN) as defined by local laboratory reference range, regular monitoring of absolute lymphocyte counts is recommended. Additional factors that might further augment the individual PML risk should be considered (see also Progressive Multifocal Leukoencephalopathy below).
- In all cases of lymphopenia, lymphocyte counts should be followed until recovery.

- 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.

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 dimethyl fumarate delayed-release capsules than in patients that received placebo. The increased incidence of elevations of hepatic transaminases in patients treated with dimethyl fumarate delayed-release capsules relative to placebo was primarily seen during the first 6 months of treatment (see 8 ADVERSE REACTIONS).

Prior to initiating treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules, 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 Sandoz Dimethyl Fumarate Delayed-Release Capsules if clinically significant liver injury induced by dimethyl fumarate is suspected.

Clinically significant cases of liver injury have been reported in patients treated with dimethyl fumarate delayed-release capsules in the postmarketing setting. The onset has ranged from a few days to several months after initiation of treatment with dimethyl fumarate delayed-release capsules. 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.

Immune

Infections: Treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules should not be initiated in patients with signs and symptoms of a serious infection.

Decreases in lymphocyte counts observed in patients treated with dimethyl fumarate delayed-release capsules 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 Sandoz Dimethyl Fumarate Delayed-Release Capsules should be considered, until the infection(s) resolves.

Herpes Zoster and Other Serious Opportunistic Infections: Cases of herpes zoster have occurred with dimethyl fumarate delayed-release capsules. The majority of cases were non-serious, however, serious cases, including disseminated herpes zoster, herpes zoster ophthalmicus, herpes zoster meningoencephalitis and herpes zoster meningomyelitis have been reported. These events may occur at any time during treatment. Monitor patients taking Sandoz Dimethyl Fumarate Delayed-Release Capsules for signs and symptoms of herpes zoster. If herpes zoster occurs, appropriate treatment for herpes zoster should be administered.

Other serious opportunistic infections have occurred with dimethyl fumarate delayed-release capsules, including cases of serious viral (herpes simplex virus, West Nile virus, cytomegalovirus), fungal (Candida and Aspergillus), and bacterial (Nocardia, Listeria monocytogenes, Mycobacterium tuberculosis) infections. These infections have been reported in patients with reduced absolute lymphocyte counts (ALC) as well as in patients with normal ALC. These infections have affected the brain, meninges, spinal cord, gastrointestinal tract, lungs, skin, eye, and ear. Patients with symptoms and signs consistent with any of these infections should undergo prompt diagnostic evaluation and receive appropriate treatment.

Consider withholding Sandoz Dimethyl Fumarate Delayed-Release Capsules treatment in patients with serious infections until the infection has resolved (See 8 ADVERSE REACTIONS, 8.5 Post Market Adverse Reactions).

Vaccination: The safety of administration of live attenuated vaccines during treatment with dimethyl fumarate delayed-release capsules have not been evaluated in clinical trials. Live vaccines have a potential risk of clinical infection and are not recommended during treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules.

The efficacy of live attenuated vaccines administered during treatment with dimethyl fumarate delayed-release capsules has not been evaluated in clinical trials.

Hypersensitivity and Anaphylactic Reactions: In clinical trials, 3 patients out of a total of 2,560 patients treated with dimethyl fumarate delayed-release capsules 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 8 ADVERSE REACTIONS, 8.5 Post Market Adverse Reactions). These reactions generally occurred after the first dose, but may occur at any time during treatment, and may be serious and life threatening. Prescribers and patients should be alert to this possibility in the event of severe flushing reaction. Patients should be instructed to discontinue Sandoz Dimethyl Fumarate Delayed-Release Capsules and seek immediate medical care should they experience signs and symptoms

of anaphylaxis or angioedema. Treatment should not be restarted.

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 Sandoz Dimethyl Fumarate Delayed-Release Capsules may decrease lymphocyte counts (see 7 WARNINGS AND PRECAUTIONS, Hematologic; 8 ADVERSE DRUG REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). A CBC, including lymphocytes, is recommended after 6 months, then every 6 to 12 months, and as clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Hematologic; 8 ADVERSE DRUG REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

Urinalysis should be performed before initiating treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules, 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 Sandoz Dimethyl Fumarate Delayed-Release Capsules. During treatment, evaluation of transaminases is recommended after 6 months of treatment, then every 6 to 12 months and as clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary; 8 ADVERSE DRUG REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with dimethyl fumarate delayed-release capsules, in the presence of lymphopenia (<0.91 x 109/L), including in patients who had not previously taken or were not concomitantly taking either immunosuppressive or immunomodulatory medications (see Adverse Reactions, Post-Marketing Experience). These PML cases have occurred predominantly in the setting of prolonged moderate to severe lymphopenia. 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, Sandoz Dimethyl Fumarate Delayed-Release Capsules 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 Sandoz Dimethyl Fumarate

Delayed-Release Capsules and as a precaution, interruption of Sandoz Dimethyl Fumarate Delayed-Release Capsules should be considered in patients with lymphocyte counts <0.5 x 10^9/L persisting for more than 6 months (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

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 dimethyl fumarate delayed-release capsules compared to patients that received placebo. The significance of these clinical observations is not known at this time.

Prior to initiating treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules, 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 dimethyl fumarate delayed-release capsules 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 Sandoz Dimethyl Fumarate Delayed-Release Capsules is used in patients receiving chronic treatment with such medications.

Vascular Disorders
Sandoz Dimethyl Fumarate Delayed-Release Capsules 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 dimethyl fumarate delayed-release capsule treated patients, compared to 5% of patients that received placebo, experienced flushing. Flushing symptoms generally began soon after initiating dimethyl fumarate 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 7 WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity; 8 ADVERSE REACTIONS, 8.5 Post Market Adverse Reactions).

Administration of Sandoz Dimethyl Fumarate Delayed-Release Capsules 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 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dose Adjustment). The long-term use of acetylsalicylic acid is not recommended for the management of flushing (see 9 DRUG INTERACTIONS).

7.1 Special Populations

Hepatic Impairment: The safety of dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules. Caution should be exercised when treating these patients (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary; 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; 8 ADVERSE DRUG REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data; 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations).

Renal Impairment: The safety of dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules. Caution should be exercised when treating these patients (see 7 WARNINGS AND PRECAUTIONS, Renal, Monitoring and Laboratory Tests; 8 ADVERSE DRUG REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data; 4 DOSAGE AND ADMINISTRATION, Dosing Considerations).

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of dimethyl fumarate delayed-release capsules in pregnant women. The use of Sandoz Dimethyl Fumarate Delayed-Release Capsules 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 teratogenicity. There were no fertility effects in male and female rats at exposures of 9 and 6 times the RHD, respectively (based on mg/m^2). 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 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

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 Sandoz Dimethyl Fumarate Delayed-Release Capsules is administered to a nursing woman.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of dimethyl fumarate delayed-release capsules in patients younger than 18 years of age have not been evaluated. Sandoz Dimethyl Fumarate Delayed-Release Capsules is not indicated in patients below 18 years of age.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Clinical studies of dimethyl fumarate delayed-release capsules did

not include sufficient numbers of patients aged 65 and over to determine whether the safety and efficacy of dimethyl fumarate delayed-release capsules may differ in elderly patients compared to younger patients. Physicians who choose to treat geriatric patients should consider that treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules 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 10 CLINICAL PHARMACOLOGY, Special Populations, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

In placebo-controlled and uncontrolled clinical studies, a total of 2,513 patients have received dimethyl fumarate delayed-release capsules; of these, n = 1169 have received at least 5 years of treatment with dimethyl fumarate delayed-release capsules, and n= 426 have received at least 10 years. The experience in uncontrolled clinical trials is consistent with the experience in the placebo-controlled clinical trials.

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

The most common adverse reactions (incidence > 10%) for patients treated with dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules were flushing (3%) and gastrointestinal events (4%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 1 lists treatment emergent adverse events that occurred during active treatment in ≥1% of dimethyl fumarate delayed-release capsule-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 Dimethyl Fumarate Treated Patients and at ≥1% Higher Rate than for Placebo

Adverse Event	Placebo N=771 (%)	Dimethyl Fumarate Delayed-Release Capsules 240 mg BID N=769 (%)
Blood and Lymphatic System Disorders Lymphopenia	2 (0.3%)	18 (2.3%)
Lymphocyte Count Decreased	1 (0.1%)	9 (1.2%)
Endocrine Disorders Microalbuminuria	24 (3.1%)	35 (4.6%)
Gastrointestinal Disorders Diarrhea	83 (10.8%)	107 (13.9%)
Nausea	67 (8.7%)	93 (12.1%)
Abdominal Pain Upper	45 (5.8%)	76 (9.9%)
Abdominal Pain	37 (4.8%)	73 (9.5%)
Vomiting	37 (4.8%)	65 (8.5%)
Dyspepsia	20 (2.6%)	35 (4.6%)
Gastritis	11 (1.4%)	22 (2.9%)
Abdominal Discomfort	11 (1.4%)	19 (2.5%)
Gastrointestinal Disorder	8 (1.0%)	18 (2.3%)
Dry Mouth	6 (0.8%)	16 (2.1%)
General Disorders and Administration Site Conditions Feeling Hot	2 (0.3%)	15 (2.0%)
Immune system Disorders Dermatitis Allergic	5 (0.6%)	13 (1.7%)
Hypersensitivity	2 (0.3%)	11 (1.4%)
Infections and Infestations Nasopharyngitis	159 (20.6%)	170 (22.1%)
Upper Respiratory Tract Infection	87 (11.3%)	99 (12.9%)
Gastroenteritis	28 (3.6%)	42 (5.5%)
Otitis Media	1 (0.1%)	10 (1.3%)
Investigations Albumin Urine Present	27 (3.5%)	46 (6.0%)
Alanine Aminotransferase Increased	38 (4.9%)	45 (5.9%)
Aspartate Aminotransferase Increased	18 (2.3%)	33 (4.3%)
Blood Urine Present	7 (0.9%)	16 (2.1%)
Blood Parathyroid Hormone Increased	6 (0.8%)	15 (2.0%)
White Blood Cell Count Decreased	1 (0.1%)	13 (1.7%)

Adverse Event	Placebo N=771 (%)	Dimethyl Fumarate Delayed-Release Capsules 240 mg BID N=769 (%)
Weight Decreased	3 (0.4%)	11 (1.4%)
Nervous System Disorders		
Burning Sensation	13 (1.7%)	21 (2.7%)
Respiratory, Thoracic and Mediastinal Disorders		
Rhinorrhoea	8 (1.0%)	15 (2.0%)
Renal and Urinary Disorders		
Urinary Tract Infection	95 (12.3%)	107 (13.9%)
Proteinuria	59 (7.7%)	67 (8.7%)
Skin and Subcutaneous Tissue Disorders		
Pruritus	30 (3.9%)	62 (8.1%)
Rash	26 (3.4%)	58 (7.5%)
Erythema	10 (1.3%)	36 (4.7%)
Dysaesthesia	5 (0.6%)	12 (1.6%)
Vascular Disorders		
Flushing	33 (4.3%)	265 (34.5%)
Hot Flush	16 (2.1%)	52 (6.8%)

Flushing: In the placebo-controlled trials, 34% of dimethyl fumarate delayed-release capsule 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 dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules (see 7 WARNINGS AND PRECAUTIONS, Vascular and 4 DOSAGE AND ADMINISTRATION).

Gastrointestinal: In placebo controlled clinical trials, 48% of patients treated with dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules compared with placebo. Four percent (4%) of patients treated with dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal Disorders and 4 DOSAGE AND ADMINISTRATION).

Infections: The incidence of infections (60% vs. 56%) and serious infections (2% vs. 1%) was similar in patients treated with dimethyl fumarate delayed-release capsules or placebo, respectively (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Infections; 8 ADVERSE DRUG REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

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 dimethyl fumarate delayed-release capsules compared to 31% of patients on placebo.

Aspartate aminotransferase (AST) >1 x ULN and <3 x ULN occurred in 24% of patients treated with dimethyl fumarate delayed-release capsules compared to 19% of patients on placebo. The increased incidence of elevations of hepatic transaminases in patients treated with dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules 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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary, Monitoring and Laboratory Tests; 8 ADVERSE DRUG REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

Renal: Adverse events of proteinuria (proteinuria, microalbuminuria and urine albumin present) were reported at slightly higher frequencies in patients treated with dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules (43%) and placebo-treated patients (40%). Typically, laboratory observations of proteinuria were not progressive. Positive urine ketones occurred more frequently in patients treated with dimethyl fumarate delayed-release capsules than in patients who received placebo, but were not associated with increases in other renal/urinary adverse events (see 8 ADVERSE DRUG REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.

8.3 Less Common Clinical Trial Adverse Reactions

The following is a list of treatment-emergent adverse events reported by patients treated with dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules, they were not necessarily caused by dimethyl fumarate delayed-release capsules.

Events are listed by system organ class in decreasing order of incidence in dimethyl fumarate delayed-release capsule 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, breast cancer (events occurred during open-label extension studies)

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial 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 dimethyl fumarate delayed-release capsules, 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 dimethyl fumarate delayed-release capsules. 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 dimethyl fumarate delayed-release capsules therapy (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

Clinical Chemistry

- In the placebo-controlled studies, measurement of urinary ketones (1+ or greater) was higher in patients treated with dimethyl fumarate delayed-release capsules (45%) compared to placebo (10%). No untoward clinical consequences were observed in clinical trials (see 8 ADVERSE REACTIONS, Renal).
- Levels of 1,25-dihydroxyvitamin D decreased in dimethyl fumarate delayed-release capsule 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 dimethyl fumarate delayed-release capsule 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.

8.5 Post-Market Adverse Reactions

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

Progressive multifocal leukoencephalopathy has occurred in the setting of lymphopenia (<0.91 x 109/L) following dimethyl fumarate delayed-release capsules administration. These PML cases have occurred predominantly in the setting of prolonged moderate to severe lymphopenia.

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

Herpes zoster infection has been reported with dimethyl fumarate delayed-release capsule administration in post marketing experience. The majority of cases were non serious.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In humans, 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).

9.4 Drug-Drug Interactions

The drugs listed in Table 2 are based on either drug interaction case reports (C) or studies (CT), or potential interactions (T) due to the expected magnitude and seriousness of the interaction (i.e., thoseidentified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence*	Effect	Clinical comment
Other fumaric acid derivatives (Topical or systemic)	T	-	During treatment with dimethyl fumarate delayed-release capsules, simultaneous use of other fumaric acid derivatives (topical or systemic) is not recommended.

Proper/Common name	Source of Evidence*	Effect	Clinical comment
Interferon beta-1a(Intramuscular)	CT	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 Dimethyl fumarate delayed-release capsules and didnot alter the pharmacokinetic profile of dimethyl fumarate delayed-release capsules.	Sandoz Dimethyl Fumarate Delayed-Release Capsules is not indicated for concomitant use with these drugs.
Glatiramer acetate (GA) (Intramuscular)	CT	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 dimethyl fumarate delayed-release capsules and didnot alter the pharmacokinetic profile of dimethyl fumarate delayed-release capsules.	Sandoz Dimethyl Fumarate Delayed-Release Capsules is not indicated forconcomitant use with these drugs.
Non-enteric coated acetylsalicylic acid	CT	Non-enteric coated acetylsalicylic acid 325 mg, when administered approximately 30 minutes before dimethyl fumarate delayed-release capsules, over 4 days of dosing in healthy adult volunteers, did not alter the pharmacokinetic profile of dimethyl fumarate delayed-release capsules, 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 withacetylsalicylic acid therapy should be considered prior toco-administration with Sandoz Dimethyl Fumarate Delayed-Release Capsules.

Proper/Common name	Source of Evidence*	Effect	Clinical comment
Monophasic combined oral contraceptive (norgestimate andethinyl estradiol)	CT, T	In a 2-period cross-over pharmacokinetic study in healthy female subjects (n=40), co-administration of dimethyl fumarate delayed-release capsules for 21 days (240 mg BID) with a monophasic combined oral contraceptive (250 µg norgestimateand 35 µg ethinyl estradiol) did not elicit any relevant effects on oral contraceptive exposure (Day 21). No interaction studies have been performed with oral contraceptives containing other progestogens, however an effect of dimethyl fumarate delayed-release capsules ontheir exposure is not expected, based on in vitro CYP induction studies (see 9.2 Drug Interactions Overview).	An effect of Sandoz Dimethyl Fumarate Delayed-Release Capsules on the exposure of oral contraceptives is not expected
Anti-neoplastic, immuno-suppressive or immune modulating drugs	T	Dimethyl fumarate delayed-release capsules has not been studied in patients treated with anti-neoplasticor immunosuppressive therapies and concomitant treatment is not recommended in these patients dueto the potential risk of additive immune system effects.	Concomitant treatment is notrecommended. Caution should also be exercised when switching patients from long-acting therapies with immune effectsto avoid additive immune system effects (see 7 WARNINGS AND PRECAUTIONS, Hematologic).
Vaccines	T	The use of live attenuated vaccines may carry the risk of infection and isnot recommended. No clinical data are available on the efficacy and safety of live attenuated vaccines inpatients taking Dimethyl fumarate delayed-release capsules.	The use of live attenuated vaccines in patients taking Sandoz Dimethyl Fumarate Delayed-Release Capsules is not recommended.

Proper/Common name	Source of Evidence*	Effect	Clinical comment
Drugs associated with nephrotoxicity	T	The use of dimethyl fumarate delayed-release capsules in patients who receive chronic treatment withdrugs that are associated with potential nephrotoxic risk (e.g., aminoglycosides, diuretics, NSAIDs, lithium) has not been evaluated.	Caution should be exercised ifSandoz Dimethyl Fumarate Delayed-Release Capsules is used in these patients (see 7 WARNINGS AND PRECAUTIONS, Renal; 8 ADVERSE REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings).
Corticosteroids	CT	In the multiple sclerosis clinical trials, relapses were treated with ashort 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.	Patients should be reminded of the potential increased riskof infection due to additive immune system effects of corticosteroids.

* Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Food does not have a clinically significant effect on exposure of dimethyl fumarate delayed-release capsules. Sandoz Dimethyl Fumarate Delayed-Release Capsules may be taken with or without food.

10 CLINICAL PHARMACOLOGY

10.1 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 dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not known.

10.2 Pharmacodynamics

The primary pharmacodynamic response to dimethyl fumarate 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 TH2 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 4 DOSAGE AND ADMINISTRATION).

In a clinical study in patients with relapsing forms of MS, patients treated with dimethyl fumarate delayed-release capsules and non-pegylated interferons mounted comparable immune responses to recall antigen (re-exposure with tetanus toxoid) inactivated neoantigen (first vaccination with conjugated meningococcal C polysaccharide vaccine), while the immune response to different serotypes of an unconjugated 23-valent pneumococcal polysaccharide vaccine varied in both treatment groups. Small numerical differences in the response to tetanus toxoid and pneumococcal serotype 3 polysaccharide were noted in favour of non-pegylated interferon.

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

10.3 Pharmacokinetics

Orally administered dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules. Therefore all pharmacokinetic analyses related to dimethyl fumarate were performed with plasma MMF concentrations.

Pharmacokinetic data were obtained in subjects with multiple sclerosis and healthy volunteers.

Table 3 - Summary of monomethyl fumarate (MMF) pharmacokinetic parameters in adult patientpopulation

	C_{max}	Tmax	$t_{½}$ (h)	AUC_{0-24}	CL	V_d
Single dose Mean	1.87 mg/L [1]	7.9 h [2]	1 h	8.21 h.mg/L [3]	68.5 L/h	134.6 L
	[1] Median C_{max} : 1.72 mg/L [2] Median T_{max} : 5 h [3] Median AUC_{0-24} : 8.02 h.mg/L					

Table 4 - Summary of monomethyl fumarate (MMF) pharmacokinetic parameters in pediatric patient population (aged 13 to 17 years)

	C_{max}	T_{max}	$t_{½}$	AUC_{0-24}	CL	V_d
Single dose Mean	2.00 mg/L	4.2 h	0.84 h	7.24 h.mg/L [1]	74.45 L/h	98.2 L
	[1] AUC_{0-12} : 3.62 h.mg/L					

Absorption

Dimethyl fumarate delayed-release capsules concentration-time profiles are characterized by high inter-individual variability. The T_{max} of dimethyl fumarate delayed-release capsules is 2-5 hours. As dimethyl fumarate 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 dimethyl fumarate delayed-release capsules. Therefore, Sandoz Dimethyl Fumarate Delayed-Release Capsules 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 dimethyl fumarate

delayed-release capsules varies between 53 and 73 L in healthy subjects. Human plasma protein binding of MMF generally ranges between 27% - 40%.

Metabolism
In humans, dimethyl fumarate delayed-release capsules 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 dimethyl fumarate 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 dimethyl fumarate delayed-release capsules at the therapeutic regimen.

Linearity
Dimethyl fumarate delayed-release capsules 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:** Sandoz Dimethyl Fumarate Delayed-Release Capsules is not indicated in patients below the age of 18. The pharmacokinetic profile of dimethyl fumarate delayed-release capsules 240 mg twice a day was evaluated in a small, open-label, uncontrolled study in patients with RRMS aged 13 to 17 years (n=22; 21 patients of whom were in the pharmacokinetic analysis). The pharmacokinetics of dimethyl fumarate delayed-release capsules in these adolescent patients was consistent with that previously observed in adult patients (Cmax: 2.00±1.29 mg/l; AUC0-12hr: 3.62±1.16 h.mg/l, which corresponds to an overall daily AUC of 7.24 h.mg/l).

- **Geriatrics:** The pharmacokinetics in patients aged 65 and over has not been studied (see 7 WARNINGS AND PRECAUTIONS, Special Populations – Geriatrics).

- **Sex:** Gender and age did not have a statistically significant impact on C_{max}.

- **Ethnic Origin:** Race and ethnicity have no effect on the pharmacokinetics of dimethyl fumarate delayed-release capsules.

- **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 7 WARNINGS AND PRECAUTIONS, Special Populations – Hepatic Impairment).

- **Renal Insufficiency:** Since the renal pathway is a secondary route of elimination for dimethyl fumarate delayed-release capsules accounting for less than 16% of the dose administered, evaluation of pharmacokinetics in individuals with renal impairment was not conducted (see 7 WARNINGS AND PRECAUTIONS, Special Populations – Renal Impairment).

- **Obesity:** 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.

11 STORAGE, STABILITY AND DISPOSAL

Store Sandoz Dimethyl Fumarate Delayed-Release Capsules (dimethyl fumarate) capsules between 15 and 30°C in the original packaging in order to protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

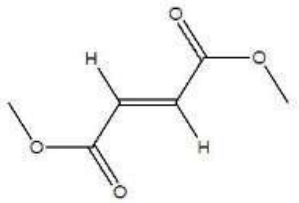
Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Dimethyl fumarate
Chemical name:	Dimethyl (2E)-but-2-enedioate
CAS:	624-49-7
Molecular formula and molecular mass:	$C_6H_8O_4$, molecular mass 144.13 g/mol
Structural formula:	



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

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 5- Summary of patient demographics for clinical trials in patients with relapsing-remitting multiple sclerosis (RRMS)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) (years)	Sex
Study 1 (DEFINE)	Randomized, double- blind, placebo-controlled study.	Dimethyl fumarate delayed-release capsules 240 mg twice or three times daily, or placebo, (oral). 2 year study.	Dimethyl fumarate delayed-release capsules BID: n=410 Dimethyl Fumarate TID: n=416 Placebo: n=408	39 (18 – 56)	Male: 26% Female: 74%
Study 2 (CONFIRM)	Multicenter, randomized,	Dimethyl fumarate delayed-release	Dimethyl fumarate	37 (18 – 56)	Male: 30% Female:

Study #	Study design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) (years)	Sex
	double- blind, placebo controlled study with a rater-blinded reference comparator of glatiramer acetate (GA).	capsules 240 mg twice or three times daily or placebo (oral), or GA. 2 year study.	delayed-release capsules BID: n=359 Dimethyl Fumarate TID: n=345 Placebo: n=363 GA: n=350		70%

The efficacy and safety of dimethyl fumarate delayed-release capsules was demonstrated in two studies that evaluated dimethyl fumarate delayed-release capsules taken either twice or three times a day in patients with relapsing-remitting multiple sclerosis (RRMS). The starting dose for dimethyl fumarate delayed-release capsules 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 (study 1 and Study 2) 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.

14.2 Study Results

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 dimethyl fumarate delayed-release capsules 240 mg twice a day (n=410), dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules than in the group that received placebo (Table 6, 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 dimethyl fumarate delayed-release capsules compared to placebo (Table 6).

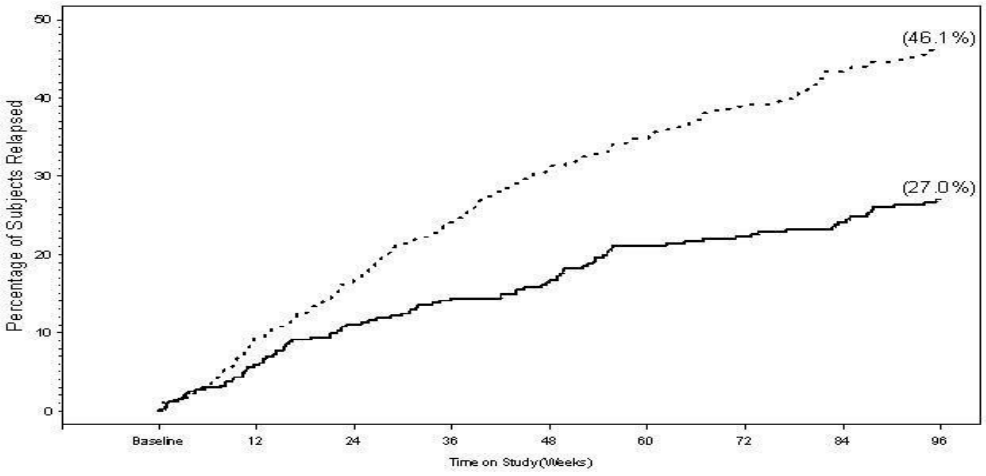
Secondary MRI endpoints included the number of new or newly enlarging T2 hyperintense lesions and number of Gd-enhancing lesions over 2 years, and both were reduced in patients treated with dimethyl fumarate delayed-release capsules compared to patients who received placebo (Table 6).

The 240 mg three times daily dose resulted in no additional benefit over the dimethyl fumarate delayed-release capsules 240 mg twice daily dose.

Table 6 – Study 1 (DEFINE) Study Results

	Dimethyl Fumarate, Delayed-Release Capsules 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



····· Placebo (n=408) ——— Dimethyl Fumarate Delayed-Release Capsules 240 mg BID (n=410)

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 dimethyl fumarate delayed-release capsules 240 mg twice a day (n=359), dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsules, 86 weeks on placebo and 88 weeks on glatiramer acetate.

The annualized relapse rate at 2 years, was significantly lower in patients treated with dimethyl fumarate delayed-release capsules than in patients treated with placebo (0.224 for dimethyl fumarate delayed-release capsules 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 dimethyl fumarate delayed-release capsule group compared to the placebo group. Time to 12-week confirmed disability progression was not significantly reduced for patients on dimethyl fumarate delayed-release capsules compared to those on placebo (Table 7).

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 dimethyl fumarate delayed-release capsules compared to those on placebo (Table 7).

Table 7 - Study 2 (CONFIRM) Study Results

	Dimethyl Fumarate Delayed-Release Capsules, 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

14.3 Comparative Bioavailability Studies

Fasting Study

A double-blind, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of Sandoz Dimethyl Fumarate Delayed-Release Capsules 240 mg delayed-release capsules (Sandoz Canada Inc.) with TECFIDERA® (dimethyl fumarate) 240 mg delayed-release capsules (Biogen Canada Inc.) was conducted in healthy, adult subjects under fasting conditions. A summary of the comparative bioavailability data from 54 subjects in presented in the following table:

Monomethyl fumarate (1 x 240 mg dimethyl fumarate) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.h/mL)	4240.14 4356.72 (24.8)	4056.49 4175.18 (24.2)	104.6	101.0 - 108.4
AUC_I (ng.h/mL)	4256.04 4372.63 (24.8)	4088.58 4203.55 (23.8)	104.2	100.7 - 107.9
C_{max} (ng/mL)	2578.44 2662.16 (26.0)	2359.60 2489.56 (33.9)	109.1	101.9 - 116.8
T_{max}§ (h)	1.75 (1.00 - 4.67)	2.25 (1.25 - 4.67)		
$T_{½}$€ (h)	0.71 (40.8)	0.77 (55.9)		

* Sandoz Dimethyl Fumarate Delayed-Release Capsules 240 mg delayed-release capsules (Sandoz Canada Inc.)
†TECFIDERA® (dimethyl fumarate) 240 mg delayed-release capsules (Biogen Canada Inc.)
§Expressed as the median (range) only
€Expressed as the arithmetic mean (CV%) only

Fed Study

A double-blind, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of Sandoz Dimethyl Fumarate Delayed-Release Capsules 240 mg delayed-release capsules (Sandoz Canada Inc.) with TECFIDERA® (dimethyl fumarate) 240 mg delayed-release capsules (Biogen Canada Inc.) was conducted on healthy, adult subjects under fed conditions. A summary of the comparative bioavailability data from 58 subjects in presented in the following table:

Monomethyl fumarate (1 x 240 mg dimethyl fumarate) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.h/mL)	4327.33 4406.88 (18.8)	4346.48 4430.71 (19.1)	99.6	96.7 - 102.6
AUC_I (ng.h/mL)	4453.10 4541.28 (19.8)	4457.02 4538.50 (18.7)	99.9	97.1 - 102.9

Monomethyl fumarate (1 x 240 mg dimethyl fumarate) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
C_{max} (ng/mL)	2778.59 3010.37 (40.2)	2663.13 2855.70 (35.3)	104.3	94.0 - 115.8
T_{max}§ (h)	4.67 (1.00 - 6.67)	3.83 (1.00 - 7.00)		
$T_{½}$€ (h)	0.83 (67.2)	0.86 (56.4)		

* Sandoz Dimethyl Fumarate Delayed-Release Capsules 240 mg delayed-release capsules (Sandoz Canada Inc.)
†TECFIDERA® (dimethyl fumarate) 240 mg delayed-release capsules (Biogen Canada Inc.)
§Expressed as the median (range) only
€Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL 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 dimethyl fumarate delayed-release 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.

Carcinogenesis: 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. TECFIDERA® dimethyl fumarate delayed-release capsules, 120 mg and 240 mg, submission control 245515, Product Monograph, Biogen Canada Inc. (OCT 07, 2021)

2. PrACH-DIMETHYL FUMARATE (dimethyl fumarate delayed-release capsules) Product Monograph, Accord Healthcare Inc., Submission Control No: 260466. Date of Revision: July 5 ,2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] Sandoz Dimethyl Fumarate Delayed-Release Capsules
Dimethyl Fumarate Delayed-Release Capsules

Read this carefully before you start taking **Sandoz Dimethyl Fumarate Delayed-Release Capsules** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Sandoz Dimethyl Fumarate Delayed-Release Capsules**.

What is Sandoz Dimethyl Fumarate Delayed-Release Capsules used for?
Sandoz Dimethyl Fumarate Delayed-Release Capsules is used in adults to treat relapsing remitting multiple sclerosis (MS). Sandoz Dimethyl Fumarate Delayed-Release Capsules helps to:

- reduce the number of flare-ups (relapses) that occur, and
- delay physical problems due to MS (disability progression).

How does Sandoz Dimethyl Fumarate Delayed-Release Capsules work?
The exact way that Sandoz Dimethyl Fumarate Delayed-Release Capsules works is not known. However, Sandoz Dimethyl Fumarate Delayed-Release Capsules is thought to work by changing the way the body's immune system works, to help keep MS from further damaging your brain and spinal cord.

What are the ingredient in Sandoz Dimethyl Fumarate Delayed-Release Capsules?
Medicinal ingredient: dimethyl fumarate

Non-Medicinal ingredients: Colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, methacrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer (1:1), silicified microcrystalline cellulose, talc, and triethyl citrate.

The capsule shell, printed with black ink, contains the following inactive ingredients: FD&C blue 1, gelatin, iron oxide black, iron oxide yellow, propylene glycol, shellac, and titanium dioxide.

Sandoz Dimethyl Fumarate Delayed-Release Capsules comes in following dosage forms:
Delayed-release capsules: 120 mg and 240 mg of dimethyl fumarate.

Do not use Sandoz Dimethyl Fumarate Delayed-Release Capsules if:

- you are allergic to dimethyl fumarate or to any other ingredients in Sandoz Dimethyl Fumarate Delayed-Release Capsules.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Dimethyl Fumarate Delayed-Release Capsules. Talk about any health conditions or problems you may have, including if you:

- have or have had low white blood cell counts (low lymphocytes).

- have a weakened immune system (immunocompromised) due to diseases (immunodeficiency syndrome), medicines, or treatments that suppress the immune system (e.g., medicines used to treat cancer or bone marrow transplantation).
- have an infection.
- have a herpes zoster infection (shingles).
- have liver problems.
- have kidney problems.
- have gastrointestinal (GI) problems (e.g., stomach or bowel problems).
- are pregnant or planning to become pregnant.
- are breast-feeding or planning to breast-feed.
- are taking other medications known as fumaric acid derivatives.
- are taking certain medications that can affect your kidney function (nephrotoxic medications).
- are planning on getting certain types of vaccines known as live attenuated vaccines. Check with your healthcare professional before receiving any vaccination during treatment or after stopping Sandoz Dimethyl Fumarate Delayed-Release Capsules.

Other warnings you should know about:

Gastrointestinal (GI) problems: Treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules can cause GI problems, especially in the first month. Some symptoms of GI problems include nausea, vomiting, diarrhea, and abdominal pain. Most people have mild to moderate symptoms and they tend to go away over time. You should take Sandoz Dimethyl Fumarate Delayed-Release Capsules with food to help reduce the chances of GI problems. If this does not help, talk to your healthcare professional. They may also temporarily reduce your dose. Do not reduce your dose unless your healthcare professional tells you to.

Infections: If you have an infection before you start taking Sandoz Dimethyl Fumarate Delayed-Release Capsules, tell your healthcare professional. Any infection that you already have may get worse. Other infections, including shingles, have occurred when taking Sandoz Dimethyl Fumarate Delayed-Release Capsules. Infections could be serious and sometimes life-threatening.

- Before you start taking Sandoz Dimethyl Fumarate Delayed-Release Capsules, your healthcare professional will make sure you have enough white blood cells (lymphocytes) in your blood. This is because Sandoz Dimethyl Fumarate Delayed-Release Capsules may cause low white blood cell count (lymphopenia). Blood measurements are done throughout treatment and afterwards, to monitor your lymphocyte count.
- While you are taking Sandoz Dimethyl Fumarate Delayed-Release Capsules if you think you have an infection, have a fever, chills or feel like you have the flu, tell your healthcare professional right away. These may be the symptoms of infection.
- If you believe your MS is getting worse (e.g. weakness, clumsiness, or visual changes) or if you notice any new or unusual symptoms, talk to your healthcare professional as soon as possible. These may be the symptoms of a rare brain disorder caused by infection called progressive multifocal leukoencephalopathy (PML). Your healthcare professional might do an MRI scan to check for this condition. Your healthcare professional will decide whether you need to stop taking Sandoz Dimethyl Fumarate Delayed-Release Capsules.

- If you need to receive medications and treatments that suppress or change how the immune system works, talk to your healthcare professional about the potential increased risk of infections.

Liver problems: Treatment with Sandoz Dimethyl Fumarate Delayed-Release Capsules may cause liver problems, including increasing certain types of liver enzymes (i.e., liver transaminases) in your body. This usually happens during the first 6 months of treatment. Your healthcare professional will monitor your liver enzyme levels before, during, and after your treatment. They may stop your treatment if you have liver problems, or if liver problems are suspected.

Flushing: Sandoz Dimethyl Fumarate Delayed-Release Capsules may cause flushing, especially at the start of your treatment. Flushing can includehot flush, warmth, redness, itching, and burning sensation. Most people have mild to moderate symptoms early in the treatment and they tend to go away over time. Your healthcare professional maytemporarily reduce your dose or recommend taking an over-the-counter pain and fever medication, such as aspirin, for a few days 30 minutes before your Sandoz Dimethyl Fumarate Delayed-Release Capsules dose. Do not reduce your dose unless your healthcare professional tells you to.

If you become flushed **and** get swelling of the face, lips, mouth or tongue, wheezing, difficulty breathing or shortness of breath, **stop taking Sandoz Dimethyl Fumarate Delayed-Release Capsules and seek emergency medical assistance.**

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Monitoring and testing: Your healthcare professional will monitor and assess your health by doing various tests. These tests may be performed before, during, and after your treatment. This will tell your healthcare professional about your blood, urine, and liver. They will use this information to determine if Sandoz Dimethyl Fumarate Delayed-Release Capsules is right for you and how it is affecting you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Sandoz Dimethyl Fumarate Delayed-Release Capsules:

- **Fumaric acid.** Sandoz Dimethyl Fumarate Delayed-Release Capsules should not be used with other types of fumaric acid. Ask your healthcare professional if you are not sure what other products may contain fumaric acids or its derivatives.
- **Medicines that affect the immune system. This can** include some commonly used cancer treatments and other medicines used to treat MS, such as, beta-interferons, glatiramer acetate, natalizumab, fingolimod, or mitoxantrone. Sandoz Dimethyl Fumarate Delayed-Release Capsules should not be started while you are on other MS medications. If you stop taking one of these medicines to switch to Sandoz Dimethyl Fumarate Delayed-Release Capsules you may be required to wait before starting Sandoz Dimethyl Fumarate Delayed-Release Capsules. The amount of time you may need to wait will vary, depending on the treatment. Your healthcare professional will know how long you may need to wait.
- **Medicines that can affect the kidneys**. This can include antibiotics from the aminoglycoside class, non-steroidal anti- inflammatory drugs (NSAIDs), diuretics, or lithium.

- **Vaccines.** If you need to receive a vaccine, talk to your healthcare professional first. The administration of vaccines containing live virus (attenuated vaccines) is not recommended.
- **Corticosteroids.** If you need to receive corticosteroids, talk to your healthcare professional about the potential increased risk of infections.
- **Acetylsalicylic acid.** Long-term use of acetylsalicylic acid (e.g., aspirin) is not recommended.

How to take Sandoz Dimethyl Fumarate Delayed-Release Capsules:

- Always follow your healthcare professional's instructions for taking Sandoz Dimethyl Fumarate Delayed-Release Capsules. You should check with your healthcare professional if you are not sure.
- **Swallow the whole Sandoz Dimethyl Fumarate Delayed-Release Capsules capsule.** Do not divide, crush, dissolve, suck, or chew the capsule.
- Sandoz Dimethyl Fumarate Delayed-Release Capsules can be taken with or without food. Taking Sandoz Dimethyl Fumarate Delayed-Release Capsules with food may help reduce the chances of certain side effects (flushing and gastrointestinal).
- Sandoz Dimethyl Fumarate Delayed-Release Capsules capsules are packaged in a folding blister card inside a carton. Remove the capsules from the blister by pushing them through the foil.
- Your healthcare professional may reduce your dose if you have certain side effects. Do not reduce your dose unless your healthcare professional tells you to.

Usual dose:

Your healthcare professional will tell you how much and how often to take Sandoz Dimethyl Fumarate Delayed-Release Capsules each day. This will depend on your condition, other medications you are taking, and how you respond to the treatment.

The usual starting and regular doses are as follows:

Starting dose: One 120 mg capsule two times a day (one in the morning and one in the evening). For a total starting daily dose of 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 two times a day (one in the morning and one in the evening). For a total regular daily dose of 480 mg a day.

Overdose:

If you think you, or a person you are caring for, have taken too much Sandoz Dimethyl Fumarate Delayed-Release Capsules, contact your healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss a dose, take it as soon as you remember if there is at least 4 hours between the morning and evening doses. If there is less than 4 hours, wait and take your next dose as planned. Do not try to make up for the missed dose by taking two doses at the same time.

What are possible side effects from using Sandoz Dimethyl Fumarate Delayed-Release Capsules?

These are not all the possible side effects you may have when taking Sandoz Dimethyl Fumarate Delayed-Release Capsules. If you experience any side effects not listed here, tell your healthcare

professional.

Side effects may include:

- Very Common - may affect more than 1 in 10 people
  urinary tract infection
- Common - may affect up to 1 in 10 people
  dry mouth
- feeling hot weight loss
  ear infection itchiness
- skin rash
- burning sensation
- Unknown frequency
- runny nose
  hair loss or thinning

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Flushing: hot flush, general swelling, rash, itchiness, warmth, redness, or burning sensation	✓		
Gastrointestinal (GI) problems: diarrhea, nausea, stomach pain, vomiting, indigestion	✓		
Infections: fever and chills, nausea, vomiting, diarrhea, or generally feeling unwell		✓	
COMMON			
Lymphopenia (low levels of white blood cells called lymphocytes): serious infections (e.g. pneumonia), or being more prone to getting infections		✓	
Proteinuria (excess proteins in the urine): frothy,foamy or bubbly urine; swelling of the face, hands, or legs; nausea; or muscle cramps at night		✓	
Liver problems (including increased levels of certain liver enzymes in the blood): loss of appetite, unusual tiredness, yellowing of the skin or eyes, dark urine, itching, nausea, or vomiting		✓	

Allergic reactions: rash, itching, difficulty breathing, difficulty swallowing, swelling of the face, lips, tongue or throat, wheezing, hives, rash			✓
RARE			
Progressive multifocal leukoencephalopathy (PML; a rare brain infection): progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, changes in thinking, memory and orientation, confusion, or personality changes			✓
UNKNOWN FREQUENCY			
Herpes zoster virus (shingles): skin rash of fluid-filled blisters, burning, itching or pain of the skin, typically on one side of the upper body or face, fever, weakness, or numbness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Sandoz Dimethyl Fumarate Delayed-Release Capsules at room temperature (between 15 to 30°C). Protect Sandoz Dimethyl Fumarate Delayed-Release Capsules 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.

If you want more information about Sandoz Dimethyl Fumarate Delayed-Release Capsules:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-

product-database.html; the manufactures website (www.sandoz.ca) or by calling the sponsor Sandoz Canada Inc. at 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc**.**

Last revised: SEP 14, 2022