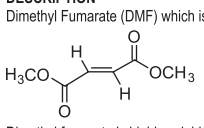
*To be sold by retail on the prescription of Specialist only*

# Dimethyl Fumarate Delayed Release Capsules 120 mg and 240 mg

**MS-120** एम एस १२०
**MS-240** एम एस २४०

COMPOSITION
Each delayed release hard gelatin capsule contains:
Dimethyl fumarate……120 mg
Each delayed release hard gelatin capsule contains:
Dimethyl fumarate……..240 mg

**DESCRIPTION**
Dimethyl Fumarate (DMF) which is also known by its chemical name, dimethyl (E) butenedioate, ($C_6H_8O_4$). It has the following structure:



Dimethyl fumarate is highly soluble in water with a molecular mass of 144.13.

**DOSAGE FORM AND STRENGTHS**
Dimethyl fumarate is available as 120 mg and 240 mg delayed release capsules for twice daily oral administration.

**INDICATIONS**
Dimethyl fumarate is indicated for the treatment of patients with relapsing forms of Multiple Sclerosis (MS).

**DOSE AND METHOD OF ADMINISTRATION**
*Dosing Information*
The starting dose for Dimethyl fumarate is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally. Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dose of 240 mg twice a day should be resumed.
Discontinuation of Dimethyl fumarate should be considered for patients unable to tolerate return to the maintenance dose. The incidence of flushing may be reduced by administration of Dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to Dimethyl fumarate dosing may reduce the incidence or severity of flushing.

*Method of administration:* Dimethyl fumarate should be swallowed whole and intact. Dimethyl fumarate should not be crushed or chewed and the capsule contents should not be sprinkled on food. Dimethyl fumarate can be taken with or without food.

Blood Tests Prior to Initiation of Therapy
Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy.

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with Dimethyl fumarate.

**USE IN SPECIAL POPULATIONS**
Pregnancy
There are no or limited amount of data from the use of dimethyl fumarate in pregnant women. Animal studies have shown reproductive toxicity. Dimethyl fumarate is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception. Dimethyl fumarate should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus.

Lactation
It is unknown whether dimethyl fumarate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Dimethyl fumarate therapy. The benefit of breast-feeding for the child and the benefit of therapy for the woman should be taken into account.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly.

Renal and hepatic impairment
Dimethyl fumarate has not been studied in patients with renal or hepatic impairment. Caution should be used when treating patients with severe renal or severe hepatic impairment

**CONTRAINDICATIONS**
Dimethyl fumarate is contraindicated in patients with known hypersensitivity to dimethyl fumarate or to any of the excipients. Reactions have included anaphylaxis and angioedema.

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

Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has also occurred in the post marketing setting in the presence of lymphopenia (<0.8x109/L) persisting for more than 6 months. While the role of lymphopenia in these cases is uncertain, the majority of cases occurred in patients with lymphocyte counts <0.5x 109/L. At the first sign or symptom suggestive of PML, withhold Dimethyl fumarate and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

MRI findings may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with other MS medications associated with PML. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Lower PML-related mortality and morbidity have been reported following discontinuation of another MS medication associated with PML in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

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

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

Elevations of hepatic transaminases (most no greater than 3 times the upper limit of normal) were observed.

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

Flushing
Dimethyl fumarate may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). Administration of Dimethyl fumarate with food may reduce the incidence of flushing. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to Dimethyl fumarate dosing may reduce the incidence or severity of flushing.

**DRUG INTERACTIONS**
Dimethyl fumarate has not been studied in combination with anti-neoplastic or immunosuppressive therapies and caution should, therefore, be used during concomitant administration.

No clinical data are available on the efficacy and safety of live attenuated vaccines in patients taking Dimethyl fumarate. Live vaccines might carry an increased risk of clinical infection and should not be given to patients treated with Dimethyl fumarate unless, in exceptional cases, this potential risk is considered to be outweighed by the risk to the individual of not vaccinating.

During treatment with Dimethyl fumarate, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided.

In humans, dimethyl fumarate is extensively metabolised by esterases before it reaches the systemic circulation and further metabolism occurs through the tricarboxylic acid 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 (a primary metabolite of dimethyl fumarate).

Commonly used medicinal products in patients with multiple sclerosis, intramuscular interferon beta-1a and glatiramer acetate, did not alter the pharmacokinetic profile of dimethyl fumarate.

Concurrent therapy with nephrotoxic medicinal products (such as aminoglycosides, diuretics, NSAIDs or lithium) may increase the potential of renal adverse reactions (e.g. proteinuria) in patients taking Dimethyl fumarate.

Consumption of moderate amounts of alcohol did not alter exposure to Dimethyl fumarate and was not associated with an increase in adverse reactions. Consumption of large quantities of undiluted strong alcoholic drinks (more than 30% alcohol by volume) may lead to increased dissolution rates of Dimethyl fumarate and, therefore, may increase the frequency of gastrointestinal adverse reactions.

In vitro CYP induction studies did not demonstrate an interaction between Dimethyl fumarate and oral contraceptives. In an in vivo study, co-administration of Dimethyl fumarate with a combined oral contraceptive (norgestimate and ethinyl estradiol) did not elicit any relevant change in oral contraceptive exposure. No interaction studies have been performed with oral contraceptives containing other progestogens; however an effect of Dimethyl fumarate on their exposure is not expected.

**UNDESIRABLE EFFECTS**
The adverse reactions are presented as MedDRA preferred terms under the MedDRA System Organ Class. The incidence of the adverse reactions below is expressed as Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1, 000 to <1/100); Rare (≥1/10, 000 to <1/1,000); Very rare (<1/10,000); Not known (frequency cannot be estimated from the available data).

| MedDRA System Organ Class | Adverse reaction | Frequency category |
|---|---|---|
| Infections and infestations | Gastroenteritis | Common |
| | Progressive multifocal leukoencephalopathy (PML) | Not known |
| Blood and lymphatic system disorders | Lymphopenia | Common |
| | Leucopenia | Common |
| Immune system disorders | Hypersensitivity | Uncommon |
| | Anaphylaxis | Unknown |
| | Dyspnoea | Unknown |
| | Hypoxia | Unknown |
| | Hypotension | Unknown |
| | Angioedema | Unknown |
| Nervous system disorders | Burning sensation | Common |
| Vascular disorders | Flushing | Very common |
| | Hot flush | Common |
| Gastrointestinal disorders | Diarrhoea | Very common |
| | Nausea | Very common |
| | Abdominal pain upper | Very common |
| | Abdominal pain | Very common |
| | Vomiting | Common |
| | Dyspepsia | Common |
| | Gastritis | Common |
| | Gastrointestinal disorder | Common |
| Hepatobiliary disorders | Aspartate aminotransferase increased | Common |
| | Alanine aminotransferase increased | Common |
| | Drug-induced liver injury | Not known |
| Skin and subcutaneous tissue disorders | Pruritus | Common |
| | Rash | Common |
| | Erythema | Common |
| Renal and urinary disorders | Proteinuria | Common |
| General disorders and administration site conditions | Feeling hot | Common |
| Investigations | Ketones measured in urine | Very common |
| | Albumin urine present | Common |
| | White blood cell count decreased | Common |

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

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

**PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES**
(Ref: TECFIDERA® (dimethyl fumarate) delayed-release capsules, US Prescribing Information, dated December 2017)

Mechanism of Action
The mechanism by which dimethyl fumarate (DMF) exerts its therapeutic effect in multiple sclerosis is unknown. DMF and the metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist *in vitro*.

*Pharmacodynamics*
Effect on immune system
Dimethyl fumarate demonstrated anti-inflammatory and immunomodulatory properties. Dimethyl fumarate and monomethyl fumarate, the primary metabolite of dimethyl fumarate, significantly reduced immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli in preclinical models.
Effect on cardiovascular system
Single doses of 240 mg or 360 mg Dimethyl fumarate did not have any effect on the QTc interval when compared to placebo in a QTc study.
*Pharmacokinetics*
After oral administration of Dimethyl fumarate, dimethyl fumarate undergoes rapid presystemic hydrolysis by esterases and is converted to its active metabolite, monomethyl fumarate (MMF). Dimethyl fumarate is not quantifiable in plasma following oral administration of Dimethyl fumarate Delayed Release capsules. Therefore all pharmacokinetic analyses related to Dimethyl fumarate Delayed Release capsules were performed with plasma MMF concentrations.
Absorption
The median $T_{max}$ of MMF is 2-2.5 hours. The peak plasma concentration ($C_{max}$) and overall exposure (AUC) increased approximately dose proportionally in the dose range studied (120 mg to 360 mg). Following administration of Dimethyl fumarate 240 mg twice a day with food, the mean $C_{max}$ of MMF was 1.87 mg/L and AUC was 8.21 mg.hr/L in MS patients.
A high-fat, high-calorie meal did not affect the AUC of MMF but decreased its $C_{max}$ by 40%. The Tmax was delayed from 2.0 hours to 5.5 hours. In this study, the incidence of flushing was reduced by approximately 25% in the fed state.
Distribution
The apparent volume of distribution of MMF varies between 53 and 73 L in healthy subjects. Human plasma protein binding of MMF is 27-45% and independent of concentration.
Metabolism
In humans, dimethyl fumarate is extensively metabolized by esterases, which are ubiquitous in the gastrointestinal tract, blood, and tissues, before it reaches the systemic circulation. Further metabolism of MMF occurs through the tricarboxylic acid (TCA) cycle, with no involvement of the cytochrome P450 (CYP) system. MMF, fumaric and citric acid, and glucose are the major metabolites in plasma.
Elimination
Exhalation of CO2 is the primary route of elimination, accounting for approximately 60% of the Dimethyl fumarate dose. Renal and fecal elimination are minor routes of elimination, accounting for 16% and 1% of the dose respectively. Trace amounts of unchanged MMF were present in urine.
The terminal half-life of MMF is approximately 1 hour and no circulating MMF is present at 24 hours in the majority of individuals. Accumulation of MMF does not occur with multiple doses of Dimethyl fumarate.

Specific Populations
Body weight, gender, and age do not require dosage adjustment.
No studies have been conducted in subjects with hepatic or renal impairment. However, neither condition would be expected to affect exposure to MMF and therefore no dosage adjustment is necessary.

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

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

**INCOMPATIBILITIES**
Not applicable

**PACKING INFORMATION**
1×14 Blister packs.

**STORAGE AND HANDLING INFORMATION**
**Do not store above 30°C.** Protect the capsules from light. Store in original container.

Keep out of reach of children

Manufactured by:
**MSN Laboratories Private Limited,**
Formulation Division, Unit-II,
Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

D03289-02