Part VI: Summary of the risk management plan

Summary of risk management plan for

Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg

(Dimethyl fumarate)

This is a summary of the risk management plan (RMP) for Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg. The RMP details important risks of Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg, how these risks can be minimised, and how more information will be obtained about Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg risks and uncertainties (missing information).

Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg should be used.

I. The medicine and what it is used for

Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg is authorised for relapsing-remitting multiple sclerosis (see SmPC for the full indication). It contains dimethyl fumarate as the active substance, and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of *Dimethyl fumarate*, together with measures to minimise such risks and the proposed studies for learning more about *Dimethyl fumarate*'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. prescription only medicine) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Dimethyl fumarate. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

Summary of safety concerns	
Important identified risks	• PML • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury
Important potential risks	• Serious and opportunistic infections (other than PML and herpes zoster) • Malignancies • Effects on pregnancy outcome • Interaction with nephrotoxic medications leading to renal toxicity
Areas of missing information	• Long-term efficacy and safety • Safety profile in patients over the age of 55 years • Safety profile in patients with moderate to severe renal impairment • Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

II.B Summary of important risks

The safety information in the proposed Product Information (SPC and PIL) of Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg is aligned to the reference medicinal product.

Important Identified Risk(s)	
PML	
Evidence for linking the risk to the medicine	PML case definitions (which categorise cases into Level 1 to Level 5) allow classification of cases based on various levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out (Level 5) as well as high and low suspect cases (Levels 2 and 3, respectively) and includes a category for cases with insufficient data despite exhaustive due diligence (Level 4). Following this adjudication process, confirmed PML cases (Level 1) have been identified in association with Dimethyl fumarate use (and other products containing fumarates) in the setting of lymphopenia

Important Identified Risk(s)	
	(< 0.91 × 10^9/L). Consequently, PML was added as a contraindication in Section 4.3 (*Contraindications*) and a listed ADR in Section 4.8 (*Undesirable effects*) of the Dimethyl fumarate SmPC, and wording relating to the detection and management of PML was implemented in Section 4.4 (*Special warnings and precautions for use*).
Risk factors and risk groups	PML can only occur in the presence of a JCV infection, with studies indicating that approximately 60% - 70% of MS patients were seropositive when screened for anti-JCV antibody [Olsson 2013]. Whilst patients who are anti-JCV antibody positive are at greater risk for developing PML than the overall population of MS patients, patients who are anti-JCV antibody negative may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. There are several well-recognised risk factors for PML such as immunosuppression, use of natalizumab, and a decrease in CD4 cells. Furthermore, there are populations that have a higher risk of developing PML, including HIV patients; patients with malignancies; and patients diagnosed with SLE, sarcoidosis, autoimmune vasculitis, non-Hodgkin's lymphoma, CLL, and bone marrow transplant. The common presentation in all confirmed cases of PML in Dimethyl fumarate -treated patients to date has been lymphopenia (< 0.91 × 10^9/L), with the majority of confirmed cases of PML occurring in the setting of moderate to severe lymphopenia for longer than 6 months' duration. Therefore, it is considered that in Dimethyl fumarate -treated patients, lymphopenia is a risk factor. Information from studies evaluating lymphopenia associated with Dimethyl fumarate treatment have shown that ALC was highly correlated with total T, CD4+ and CD8+ T cells, highlighting the effectiveness of regular monitoring of lymphocyte counts in identifying patients at risk of developing lymphopenia. Additional factors that might contribute to an increased risk for PML in the setting of lymphopenia are duration of Dimethyl fumarate therapy (cases of PML have occurred after approximately 1 to 5 years of treatment, although the exact relationship with duration of treatment is unknown); profound decreases in CD4+ and especially in CD8+ T cell counts, which are important for immunological defence; and prior immunosuppressive or immunomodulatory therapy. Additionally, the majority of PML cases in the postmarketing setting have occurred in patients > 50 years of age.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.3, 4.4, and 4.8 and PL Section 4. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** None

Important Identified Risk(s)	
Decreases in leukocyte and lymphocyte counts	
Evidence for linking the risk to the medicine	In placebo-controlled studies, most patients (> 98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with Dimethyl fumarate, mean lymphocyte counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% of baseline value. Overall, mean and median lymphocyte counts remained within normal limits; however, lymphocyte counts of $< 0.5 \times 10^9$/L were observed in < 1% of patients treated with placebo and 6% of patients treated with Dimethyl fumarate . Consequently, leukopenia and lymphopenia are included as ADRs in Section 4.8 (*Undesirable effects*) of the Dimethyl fumarate SmPC, and requirements for regular monitoring of complete blood cell counts, including lymphocytes, are included in Section 4.4 (*Special warnings and precautions for use*).
Risk factors and risk groups	Analyses of clinical trial data from participants treated with Dimethyl fumarate suggest that the majority of the participants in this subpopulation who are at risk for developing lymphopenia tended to present early with lymphocyte counts $< 0.5 \times 10^9$/L, specifically within the first 6 to 12 months of Dimethyl fumarate treatment.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.4 and 4.8 and PL Section 4. • Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Drug-induced liver injury	
Evidence for linking the risk to the medicine	In placebo-controlled studies, elevations of hepatic transaminases were observed. The majority of patients with elevations had hepatic transaminases that were < 3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase ≥ 3 times ULN, respectively, were seen in 5% and 2% of patients treated with placebo and 6% and 2% of patients treated with Dimethyl fumarate . Elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN, were not observed in placebo-controlled studies. Nevertheless, increase of liver enzymes and cases of DILI (elevations in transaminases ≥ 3 times ULN with concomitant elevations in total bilirubin > 2 times ULN), have been reported during postmarketing experience following Dimethyl fumarate administration, which resolved upon treatment discontinuation. Consequently, DILI is included as an ADR in Section 4.8 (*Undesirable effects*) of the Dimethyl fumarate SmPC, and advice relating to the monitoring of liver function prior to and during treatment is included in Section 4.4 (*Special warnings and precautions for use*).
Risk factors and risk groups	No risk factors have been identified.

Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.4 and 4.8 and PL Section 4. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Important Potential Risk(s)	
Serious and opportunistic infections (other than PML and herpes zoster)	
Evidence for linking the risk to the medicine	Dimethyl fumarate has been associated with a risk of severe, prolonged lymphopenia in approximately 2% of the pivotal clinical trial population, which could theoretically lead to an increased risk of serious and opportunistic infection. However, to date, the incidence of serious infections (excluding PML and herpes zoster) is similar in patients treated with placebo versus those treated with Dimethyl fumarate Therefore, excluding PML infection, no evidence of an increased risk of other serious or opportunistic infections has been demonstrated.
Risk factors and risk groups	Lymphopenia may increase the risk of serious and opportunistic infections.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 4. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Malignancies	
Evidence for linking the risk to the medicine	In 2-year rodent carcinogenicity studies with Dimethyl fumarate, renal tubular adenomas and carcinomas were observed, which were attributed to an exacerbation of rodent-specific age-related nephropathy. The nephropathy observed in aging rodents has no human correlate and since Dimethyl fumarate was not associated with an increased risk of urinary or renal events in clinical studies, these preclinical findings represent a relatively low risk to humans. From a review of all available data, no evidence of a causal link between Dimethyl fumarate and the development of malignancies has been identified, and the types and frequencies of malignancies reported in patients treated with Dimethyl fumarate are consistent with those observed in the general population.
Risk factors and risk groups	None known
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 5.3 Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.

Effects on pregnancy outcome	
Evidence for linking the risk to the medicine	In reproductive studies in rats and rabbits, DMF was not found to be teratogenic (i.e., no malformation. In the rat during organogenesis, reduction in maternal weight and foetal weights, and foetal variations of ossification (metatarsals and hindlimb phalanges) were observed. Different than malformation, variation is defined as a change that occurs within the normal population and is unlikely to adversely affect survival or health of the animal. In rabbits during organogenesis, DMF-related effects consisted of maternal weight loss and an increase incidence of abortions. In the rat during pregnancy and lactation, lower body weight in the F1 offspring, and delays in sexual maturation (preputial separation) in male offspring were observed. It is likely that the DMF effects are secondary to maternal toxicity for all the reproductive studies. Current data from clinical trials, postmarketing and ongoing Pregnancy Exposure Registry (Study 109MS402) do not suggest that Dimethyl fumarate, when taken early in pregnancy, has an adverse or negative effect on pregnancy outcome. Further characterisation is being investigated in Study 109MS402.
Risk factors and risk groups	Women of childbearing potential.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.6 and 5.3 and PL Section 2. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Interaction with nephrotoxic medications leading to renal toxicity	
Evidence for linking the risk to the medicine	Results of a subgroup analysis within the placebo-controlled studies show that there was an increased incidence of renal and urinary AEs (primarily AEs of proteinuria) in participants with concomitant PNM compared to those patients who did not receive potentially nephrotoxic drugs.
Risk factors and risk groups	MS patients receiving nephrotoxic drugs.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.5 and PL Section 2. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.

Areas of Missing Information	
Long-term efficacy and safety	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.8 and 5.1, and PL Sections 1 and 4. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Safety profile in patients over the age of 55 years	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.2 and 5.2. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Safety profile in patients with moderate to severe renal impairment	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 2. Legal status: Medicinal product subject to restricted medical prescription.
Safety profile in patients with hepatic impairment	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 2. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures
Safety profile in patients with severe active GI disease	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 and PL Section 2. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures
Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.5 and PL Section 2. Legal status: Medicinal product subject to restricted medical prescription. ***Additional risk minimisation measures*** No additional risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg.