Summary of Risk Management Plan (RMP)

Tecfidera™ (dimethyl fumarate)

Biogen Switzerland AG

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Summary of the Risk Management Plan (RMP) for Tecfidera™ (dimethyl fumarate)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Tecfidera™ is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Tecfidera™ in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Biogen Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tecfidera™.

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SUMMARY OF RISK MANAGEMENT PLAN TECFIDERA™ (DIMETHYL FUMARATE)

This is a summary of the risk management plan (RMP) for Tecfidera™. The RMP details important risks of Tecfidera how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) of Tecfidera.

The Tecfidera Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Tecfidera should be used.

This summary of the RMP for Tecfidera should be read in the context of all available relevant information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current described safety concerns will be included in updates of the RMP for Tecfidera.

I. The medicine and what it is used for

Tecfidera 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.

Further information about the evaluation of the benefits of Tecfidera can be found in the EPAR for Tecfidera including in its plain-language summary, available on the EMA website, under the medicine's webpage:

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

Important risks of Tecfidera together with measures to minimise such risks and the proposed studies for learning more about the risks of Tecfidera 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, respectively;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly; and
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) 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 Tecfidera is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Tecfidera are risks that need special risk management activities to further investigate or minimise the risk so that the medicinal product can be safely taken. Important risks can be categorised as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tecfidera. 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 needs to be collected (e.g. on the long-term use of the medicine):

List of important risks and areas of missing information	
Important identified risks	• PML • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury
Important potential risks	• Serious and opportunistic infections (other than PML) • 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 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

This section presents a summary of important identified risks, important potential risks and missing information.

Important Identified Risk(s)	
PML	
Evidence for linking the risk to the medicine	The MAH utilises a framework that uses standardised criteria and case definitions to differentiate and classify reported cases of PML by levels of diagnostic certainty. This objective adjudication process was developed with external PML expert input and has been used to evaluate PML case reports for Tysabri for several years. PML case definitions (which categorize 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

Important Identified Risk(s)	
	(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 Tecfidera use (and other products containing fumarates) in the setting of prolonged moderate to severe lymphopenia. Consequently, PML was added as a listed ADR in Section 4.8 (Undesirable effects) of the Tecfidera 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, patient 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-recognized risk factors for PML such as immunosuppression, use of Tysabri® 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. Although several hypothetical risk factors have been proposed as biomarkers to stratify PML risk, there is not clear evidence for most of these. Furthermore, relevant information from risk characterisation and studies evaluating risk factors relevant for identification of potential parameters for patients at risk (detection of mutant pathogenic JCV DNA in serum, host genetic marker, CSF IgM oligoclonal bands, serum protein signature, and CD62L/L-selectin) for developing PML in natalizumab treated patients have been conducted with no JCV-specific or host-specific biomarker identified that improves upon the current PML risk algorithm in Tysabri patients. The common presentation in all confirmed cases of PML in Tecfidera-treated patients to date have been an observed moderate to severe prolonged lymphopenia. Therefore, it is considered that in Tecfidera treated patients, prolonged moderate to severe lymphopenia is a risk factor. Information from studies evaluating lymphopenia associated with Tecfidera treatment have shown that ALC was highly correlated with total T, CD4+ and CD8+ T cells which underscore that the regular monitoring of lymphocyte counts provides an effective way to identify patients at risk of developing prolonged, moderate to severe lymphopenia.
Risk minimisation measures	***Routine risk minimisation measures:*** PML is listed as an ADR in SmPC Section 4.8 (*Undesirable effects*) and PL Section 4 (*Possible side effects*).

Important Identified Risk(s)	
	Recommendations on risk factors, detection and management of PML and information regarding the clinical presentation of PML are included in SmPC Section 4.4 (*Warnings and precautions for use*). Information regarding the clinical symptoms of PML are included in PL Section 4 *(Possible side effects).* ***Additional risk minimisation measures*** No additional risk minimisation measures.
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 Tecfidera, 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 Tecfidera. Consequently, leukopenia and lymphopenia are included as ADRs in Section 4.8 (*Undesirable effects*) of the Tecfidera 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 suggest that patients at risk for developing severe, prolonged lymphopenia can be identified early in a subset of subjects presenting with consecutive lymphocyte counts $<0.5 \times 10^9$/L for more than 6 months (approximately 2% of the trial population). The majority of the subjects in this subpopulation who are at risk for developing severe, prolonged lymphopenia tended to present early with lymphocyte counts $<0.5 \times 10^9$/L, specifically, within the first 6 to 12 months of Tecfidera treatment.
Risk minimisation measures	***Routine risk minimisation measures:*** Decreases in leucocyte and lymphocyte counts are listed as ADRs in SmPC Section 4.8 (*Undesirable effects*) and PL Section 4 (*Possible side effects*). Recommendations in SmPC Section 4.4 (*Warnings and precautions for use*) regarding the requirement for regular complete blood counts, including lymphocytes, and suggestions regarding withholding Tecfidera treatment in patients with lymphocyte counts <0.5 x 10^9/L persisting for more than 6 months. Information in PL Section 4 (*Possible side effects*) advises patients to contact their doctor immediately if they suspect they have a serious infection (such as pneumonia). ***Additional risk minimisation measures*** No additional risk minimisation measures.

Important Identified Risk(s)	
Additional pharmacovigilance activities	Long-term safety extension study (Study 109MS303) Observational study (Study 109MS401)
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 Tecfidera. 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 post marketing experience following Tecfidera administration, which resolved upon treatment discontinuation. Consequently, DILI is included as an ADR in Section 4.8 (Undesirable effects) of the Tecfidera 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:*** Drug induced liver injury listed as an ADR in SmPC Section 4.8 (*Undesirable effects*) and PL Section 4 (*Possible side effects*). Information in SmPC Section 4.4 (*Warnings and precautions for use*) regarding the clinical presentation of the reported events of drug-induced liver injury and recommendations for liver function test monitoring. Information in PL Section 4 (*Possible side effects*) advises patients to contact their doctor immediately if they have an increase in levels of liver enzymes (*ALT, AST*) in the blood. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Long-term safety extension study (Study 109MS303) Observational study (Study 109MS401)

Important Potential Risk(s)	
Serious and opportunistic infections (other than PML)	
Evidence for linking the risk to the medicine	Tecfidera has been associated with a risk of severe, prolonged lymphopenia in approximately 2% of the pivotal clinical trial population,

Important Potential Risk(s)	
	which could theoretically lead to an increased risk of serious and opportunistic infection. However, to date, the incidence of serious infections (excluding PML) is similar in patients treated with placebo versus those treated with Tecfidera Therefore, excluding PML infection, no evidence of an increased risk of other serious or opportunistic infections has been demonstrated.
Risk factors and risk groups	Prolonged and severe lymphopenia may increase the risk of serious and opportunistic infections.
Risk minimisation measures	***Routine risk minimisation measures:*** Recommendations on risk factors for opportunistic infection (moderate to severe prolonged lymphopenia) and advice on withholding Tecfidera administration if a serious infection is suspected are included in SmPC Section 4.4 (*Warnings and precautions for use*). Information in PL Section 4 (*Possible side effects*) advises patients to contact their doctor immediately if they suspect that have a serious infection. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Observational study (Study 109MS401) Long-term safety extension study (Study 109MS303)
Malignancies	
Evidence for linking the risk to the medicine	In 2-year rodent carcinogenicity studies with Tecfidera, 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 Tecfidera was not associated with an increased risk of urinary or renal events in clinical studies, these pre-clinical findings represent a relatively low risk to humans. From a review of all available data, no evidence of a causal link between Tecfidera and the development of malignancies has been identified, and the types and frequencies of malignancies reported in patients treated with Tecfidera are consistent those observed in the general population.
Risk factors and risk groups	None known
Risk minimisation measures	***Routine risk minimisation measures:*** Information regarding the findings from non-clinical carcinogenicity studies is provided in SmPC Section 5.3 (*Preclinical safety data*). ***Additional risk minimisation measures*** No additional risk minimisation measures.

Important Potential Risk(s)	
Additional pharmacovigilance activities	Observational study (Study 109MS401) Long-term safety extension study (Study 109MS303)
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, post-marketing and ongoing Pregnancy Exposure Registry (109MS402) do not suggest that Tecfidera, 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 child bearing potential.
Risk minimisation measures	***Routine risk minimisation measures:*** Information regarding the findings from non-clinical reproductive studies is provided in SmPC Section 5.3 (Preclinical safety data). Information stating Tecfidera is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception is provided in SmPC Section 4.6 (*Fertility, pregnancy and lactation*), and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Pregnancy registry (Study 109MS402)
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 subjects with concomitant potentially nephrotoxic medication (PNM) compared to those patients who did not receive potentially nephrotoxic drugs.
Risk factors and risk groups	MS patients receiving nephrotoxic drugs.

Important Potential Risk(s)	
Risk minimisation measures	***Routine risk minimisation measures:*** Information describing the potential for interactions with nephrotoxic medicinal products and the potential clinical consequences is provided in SmPC Section 4.5 (*Interaction with other medicinal products and other forms of interaction*). ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Observational study (Study 109MS401)

Areas of Missing Information	
Long term efficacy and safety	
Risk minimisation measures	***Routine risk minimisation measures:*** Text in SmPC Section 4.8 *(Undesirable effects)* describes safety profile and Section 5.1 *(Pharmacodynamic properties)* describes clinical efficacy and safety Text in PL Section 1 (*What Tecfidera is and what it is used for*) informs patients what Tecfidera is used for and how it works. Section 4 *(Possible side effects)* advises patients on side effects and informing their HCP if they experience side effects. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Long-term safety extension study (Study 109MS303) Observational study (Study 109MS401) Open-label extension (Part 2) of Study 109MS306 (in paediatric participants aged 10 to <18 years)
Safety profile in patients over the age of 55 years	
Risk minimisation measures	***Routine risk minimisation measures:*** Text in SmPC Section 4.2 (*Posology and method of administration*) and Section 5.2 (*Pharmacokinetic properties*) describes the paucity of data in patients over the age of 55 years and 65 years, respectively. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)
Safety profile in patients with renal impairment	

Areas of Missing Information	
Risk minimisation measures	***Routine risk minimisation measures:*** Text in SmPC Section 4.4 (*Special warnings and precautions for use*) advises caution when treating patients with severe renal impairment Text in PL Section 2 (*What you need to know before you take Tecfidera*) advises patients to inform their HCP if they have an existing severe kidney disease.
Additional pharmacovigilance activities	Observational study (Study 109MS401)
Safety profile in patients with hepatic impairment	
Risk minimisation measures	***Routine risk minimisation measures:*** Text in SmPC Section 4.4 (*Special warnings and precautions for use*) advises caution when treating patients with severe hepatic impairment Text in PL Section 2 (*What you need to know before you take Tecfidera*) advises patients to inform their HCP if they have an existing severe liver disease. ***Additional risk minimisation measures*** No additional risk minimisation measures
Additional pharmacovigilance activities	Observational study (Study 109MS401)
Safety profile in patients with severe active GI disease	
Risk minimisation measures	***Routine risk minimisation measures:*** Text in SmPC Section 4.4 (*Special warnings and precautions for use*) describes the paucity of data in patients with severe active gastrointestinal disease. Text in PL Section 2 (*What you need to know before you take Tecfidera*) advises patients to inform their HCP if they have an existing disease of the stomach or bowel. ***Additional risk minimisation measures*** No additional risk minimisation measures
Additional pharmacovigilance activities	Observational study (Study 109MS401)
Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies	
Risk minimisation measures	***Routine risk minimisation measures:*** Text in SmPC Section 4.5 (*Interaction with other medicinal products and other forms of interaction*).

Areas of Missing Information	
	Text in PL Section 2 (*What you need to know before you take Tecfidera*) advises patients to inform their HCP if they are taking medications that affect the body's immune system. ***Additional risk minimisation measures*** No additional risk minimisation measures
Additional pharmacovigilance activities	Observational study (Study 109MS401)

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation for Tecfidera .

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

Other studies in the post authorisation development plan are as follows:

- **Study 109MS401:**
  - *Purpose of the study:* Characterise the lo ng-term benefit-risk profile of Tecfidera (BG00012) in patients with MS who are prescribed Tecfidera under routine clinical care.
- **Study 109MS402:**
  - *Purpose of the study:* To determine any effects of exposure of BG00012 on the outcome of pregnancies.
- **Study 109MS306 Part 2:**
  - *Purpose of the study:* Evaluate the long-term safety and MS outcomes in children with MS who are aged 10 to <18 years.
- **Study 109MS303:**
  - *Purpose of the study:* Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with RRMS