Summary of Risk Management Plan (RMP)

Vumerity™ (diroximel fumarate)

Biogen Switzerland AG

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Summary of the Risk Management Plan (RMP) for Vumerity™ (diroximel 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 Vumerity™ 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 Vumerity™ 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 Vumerity™.

Summary of Risk Management Plan for Vumerity™ (diroximel fumarate)

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

Controlled pharmacokinetic studies have identified treatment regimens for Vumerity and Tecfidera that result in comparable exposure levels of the same active metabolite, monomethyl fumarate (MMF). Therefore, the established Tecfidera safety data relevant to Vumerity are used to further understand the risks associated with Vumerity.

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

This summary of the RMP for Vumerity 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 Vumerity.

I. The medicine and what it is used for

Vumerity is indicated for the treatment of adults with relapsing-remitting multiple sclerosis (RRMS) [see SmPC for the full indication]. It contains diroximel fumarate (DRF) as the active substance, and it is given orally.

Further information about the evaluation of the benefits of Vumerity can be found in the EPAR for Vumerity, including in its plain-language summary, available on the European Medicines Agency (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 Vumerity, together with measures to minimise such risks and the proposed studies for learning more about Vumerity's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL 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 the Periodic Safety Update Report assessment (after approval) 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 Vumerity is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vumerity 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 Vumerity. 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 missing information	
Important identified risks	• Progressive multifocal leukoencephalopathy (PML) • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury (DILI)
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
Missing information	• Long-term efficacy and safety • Safety profile in patients older than 65 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 antineoplastic or immunosuppressive therapies

II.B Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information. See Section II.C of this summary for an overview of the postauthorisation development plan.

Important identified risks	
PML	
Evidence for linking the risk to the medicine	Similar to Tecfidera, Vumerity has the potential to lower lymphocyte counts, and lymphopenia is a known risk factor for infections, including opportunistic infections. PML has occurred in the setting of lymphopenia (< 0.91×10^9/L) after Tecfidera administration. PML case definitions (which categorise cases into Level 1 to Level 5) allow classification of cases based on varying levels of diagnostic certainty, ranging from the highest to lowest. It outlines specific criteria for ruled-out cases (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). This adjudication process has been used to identify confirmed PML cases (Level 1) in association with Tecfidera use (and other products containing fumaric acid esters) in the setting of lymphopenia (< 0.91×10^9/L). Consequently, PML is an important identified risk for Vumerity and wording relating to the detection and management of PML is included in the Vumerity SmPC (Section 4.4 [*Special warnings and precautions for use*]).
Risk factors and risk groups	PML can only occur in the presence of a John Cunningham virus (JCV) infection, with studies indicating that approximately 60% to 70% of multiple sclerosis (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, those 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 lymphocyte count. Furthermore, some patient populations have a higher risk of developing PML, including those with human immunodeficiency virus (HIV); those with malignancies (including non-Hodgkin's lymphoma and chronic lymphocytic leukaemia [CLL]); those diagnosed with systemic lupus erythematosus (SLE), sarcoidosis, or autoimmune vasculitis; and those undergoing bone marrow transplantation. With regard to Tecfidera, the finding common to all confirmed cases of PML reported to date has been the presence of 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, in Tecfidera- and Vumerity-treated patients, lymphopenia is considered a risk factor. Information from studies evaluating lymphopenia associated with Tecfidera treatment have shown that absolute lymphocyte counts (ALC) was highly correlated with total, cluster of differentiation (CD)4+, and CD8+ T cells, highlighting the effectiveness of the regular monitoring of lymphocyte counts in identifying patients at risk of developing lymphopenia.

Important identified risks	
	Additional factors that might contribute to an increased risk for PML in the setting of lymphopenia are duration of Tecfidera 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 4.4 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
Additional pharmacovigilance activities	None
Decreases in leukocyte and lymphocyte counts	
Evidence for linking the risk to the medicine	In Study ALK8700-A301, 9.2% of participants experienced lymphocyte counts < 0.5×10^9/L (lower limit of normal [LLN] 0.91×10^9/L) and participants with lymphocyte counts of < 0.5×10^9/L for 4 weeks were discontinued from the study as per protocol. AEs associated with lymphopenia, which includes lymphopenia, decreased lymphocyte count, and leukopenia, were experienced by 17.7% of participants. AESIs relevant to lymphocytes (lymphopenia, lymphocyte count decreased, and lymphocyte percentage decreased) were experienced by 15.4% of participants Overall, lymphopenia AEs resulted in treatment discontinuation in 22 participants (14 participants because of lymphopenia [1.3%], 7 participants because of lymphocyte count decreased [0.7%], and 1 participant because of leukopenia [< 0.1%]). No serious adverse events (SAEs) of lymphopenia, lymphocyte count decreased, or lymphocyte percentage decreased were experienced during study treatment, and most AEs were mild or moderate in severity. The incidence of the first occurrence of lymphopenia was highest between 3 and 6 months of treatment and between 12 and 18 months of treatment (4.0% and 4.3%, respectively). Most participants continued in the study; 71.8% of lymphopenia AEs and 56.5% of lymphocyte count decreased AEs resolved. The findings observed in the development programme with Vumerity are consistent with those for Tecfidera. Consequently, leukopenia and lymphopenia were added as adverse drug reactions (ADRs) in Section 4.8 (*Undesirable effects*) of the Vumerity SmPC, and requirements for regular monitoring of complete blood counts (CBCs), including

Important identified risks	
	lymphocytes, were 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 Tecfidera suggest that the majority of the participants in this subpopulation who are at risk for developing lymphopenia tended to present early with lymphocyte counts < 0.5×10^9/L, specifically within the first 6 to 12 months of Tecfidera 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.
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401).
Drug-induced liver injury	
Evidence for linking the risk to the medicine	Overall, in the Vumerity Study ALK8700-A301, the incidence of treatment-emergent AEs in the liver injury category was experienced by 7.5% of participants, in whom the majority of those AEs resolved (84.8% of participants). The incidence of these AEs occurred more prominently during the first 2 months of treatment (median: 31 days), and most liver injury events were mild or moderate in severity. The most common AESI in this category was alanine aminotransferase (ALT) increased, which was experienced by 5.6% of participants. There were 2 SAEs in the category of elevated liver transaminases, both reversible. One resulted in treatment discontinuation. None of the participants receiving Vumerity had values meeting Hy's law criteria (total bilirubin ≥ 2 × ULN and ALT or AST ≥ 3 × ULN). In Tecfidera placebo-controlled studies, elevations of ALT and AST were observed. The majority of participants with elevations had elevations < 3 times the ULN. Elevations of ALT and AST ≥ 3 times the ULN, respectively, were seen in 5% and 2% of participants treated with placebo and 6% and 2% of participants treated with Tecfidera. Elevations in transaminases ≥ 3 times the ULN with concomitant elevations in total bilirubin > 2 times the ULN were not observed in placebo-controlled studies. Nevertheless, increases in liver enzymes and cases of DILI consistent with Hy's law have been reported during postmarketing experience after Tecfidera administration; these have resolved upon treatment discontinuation.
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.

Important identified risks	
	Legal status: Medicinal product subject to restricted medical prescription. ***<u>Additional risk minimisation measures:</u>*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401).
Serious and opportunistic infections (other than PML and herpes zoster)	
Evidence for linking the risk to the medicine	Cumulatively, in Vumerity studies, 9 SAEs have been reported in the Infections and infestations category (all in Study ALK8700-A301), none of which were classified as opportunistic infections. All but one of the events was assessed as unrelated to Vumerity. These SAEs included appendicitis (2), cellulitis, pharyngitis, pneumonia, pneumonia bacterial (fatal), pharyngeal abscess, sepsis, and urinary tract infection. The event of pharyngitis was assessed as possibly related to study drug by the Investigator. One participant in Study ALK8700-A301 discontinued due to a serious infection, pneumonia bacterial, which was fatal. Tecfidera has been associated with a risk of severe prolonged lymphopenia in approximately 2% of the pivotal clinical trial population (Study 109MS303), which could theoretically lead to an increased risk of serious and opportunistic infection. However, the incidence of serious infections (excluding PML and herpes zoster) is similar in participants treated with placebo versus those treated with Tecfidera. Therefore, excluding PML infection and herpes zoster, 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	***<u>Routine risk minimisation measures:</u>*** SmPC Section 4.4 and PL Section 4. Legal status: Medicinal product subject to restricted medical prescription. ***<u>Additional risk minimisation measures:</u>*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401).
Malignancies	
Evidence for linking the risk to the medicine	In Study ALK8700-A301, there were 5 reported malignancies, and no malignancy was seen in greater than one participant. 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

Important identified risks	
	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 nonclinical 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:*** SmPC Section 5.3. ***Additional risk minimisation measures*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401)
Effects on pregnancy outcome	
Evidence for linking the risk to the medicine	Reproductive toxicology studies conducted with Vumerity revealed no impairment of male and female fertility in rats, no teratogenicity in rats and rabbits, and no pre- and postnatal development toxicity in rats at MMF and 2-hydroxyethyl succinimide (HES) exposure area under the concentration-time curve (AUC) at least 2 times the recommended human dose (RHD) of Vumerity. At maternal toxic doses, the offspring of Tecfidera-treated pregnant animals exhibited skeletal variations in rats and skeletal variations/malformations in rabbits; these findings occurred at MMF AUC that was approximately 10 times the RHD of Vumerity in rats and ≥ 6 times that in rabbits. At a toxic dose to pregnant rats, with MMF exposure (AUC) that was approximately 10 times of that at the RHD of Vumerity, decreased birth weights and body weights/weight gains during the preweaning period were noted in the offspring. Except for skeletal malformations in rabbits, similar embryo-foetal developmental findings have been reported for Tecfidera. However, no adequate data exist on the developmental risk associated with the use of Vumerity in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus. Ten pregnancies have been reported in the DRF clinical study programme. One pregnancy was reported in the Phase 1 study (Study ALK8700-A110), and 9 pregnancies were reported in Study ALK8700-A301. The outcome of 6 pregnancies was the delivery of 7 healthy, full-term infants (5 singletons and 1 twin gestation); 2 pregnancies resulted in spontaneous abortions (gestational ages unknown); and 2 pregnancies were terminated by elective abortions, 1 at 8 weeks and 1 at 10 weeks of gestation.

Important identified risks	
	The impact of Vumerity on pregnancy outcomes will be evaluated in a prospective pregnancy registry (Study 272MS401). The effects of Vumerity on labour and delivery are unknown. Current data from clinical trials, postmarketing and ongoing Biogen Multiple Sclerosis Pregnancy Exposure Registry (Study 109MS402) do not suggest that Tecfidera, when taken early in pregnancy, has an adverse or negative effect on pregnancy outcome. The observations from these studies are relevant to DRF given the shared common active metabolite, MMF, with Tecfidera.
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.
Additional pharmacovigilance activities	Vumerity Pregnancy Exposure Registry.
Interaction with nephrotoxic medications leading to renal toxicity	
Evidence for linking the risk to the medicine	In Study ALK8700-A301 with DRF and as of 01 September 2020, the overall incidence of AESIs in the renal injury category was low (3.5% [37/1057] of participants). The incidence was low across all groups. All events in this category were mild or moderate in severity and nonserious, with the most common event being proteinuria, which was experienced by 1.3% (14/1057) of participants. The evaluation of the events does not suggest or provide any evidence of renal injury associated with DRF. No impact to the risk-benefit balance of DRF is anticipated. Results of a subgroup analysis within the placebo-controlled Tecfidera studies show that there was an increased incidence of renal and urinary AEs (primarily AEs of proteinuria) in participants with concomitant potentially nephrotoxic medication (PNM) compared with participants who did not receive PNMs.
Risk factors and risk groups	MS participants 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.

Important identified risks	
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401).
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
Additional pharmacovigilance activities	Observational study (Tecfidera Study109MS401). Observational registry-based safety study (Vumerity Study 272MS403).
Safety profile in patients older than 65 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.
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401).
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. ***Additional risk minimisation measures:*** No additional risk minimisation measures.
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401).
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.

Important identified risks	
	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:*** 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.
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401).
Increased risk of infection in patients concomitantly taking antineoplastic 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.
Additional pharmacovigilance activities	Observational study (Tecfidera Study 109MS401).

II.C Postauthorisation development plan

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

There are no studies that are conditions of the marketing authorisation or specific obligation of Vumerity.

II.C.2 Other studies in postauthorisation development plan

Other studies in the postauthorisation development plan are as follows:

- **Vumerity Pregnancy Exposure Registry Study 272MS401:**
  - *Purpose of the study:* To compare the maternal, foetal, and infant outcomes of women with MS exposed to Vumerity during pregnancy with 2 unexposed comparator populations.

- **Tecfidera Study 109MS401:**
  - *Purpose of the study*: To determine the incidence, type, and pattern of SAEs, including but not limited to infections (including opportunistic infections), hepatic events, malignancies, and renal events, and of AEs leading to treatment discontinuation in patients with MS treated with Tecfidera.
- **Vumerity Observational Registry-Based Safety Study 272MS403:**
  - *Purpose of the study*: To estimate the incidence rate of SAEs, including but not limited to malignancies and serious and opportunistic infections, among patients with MS treated with Vumerity or Tecfidera.