TECFIDERA

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IB/0086	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/03/2024		SmPC and PL	
PSUSA/10143 /202303	Periodic Safety Update EU Single assessment - dimethyl fumarate, diroximel fumarate (multiple sclerosis)	30/11/2023	n/a		PRAC Recommendation - maintenance

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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II/0082	Amendment of section 4.6 of the SmPC in order to update information on pregnancy based on results from study 109MS402 - Tecfidera (dimethyl fumarate) Pregnancy Exposure Registry (TecGistry), listed as a category 3 study in the RMP. This is an observational study and aims to address the safety concern of effects on pregnancy outcome and prospectively evaluates pregnancy outcomes in women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product. The Package Leaflet is updated accordingly and the MAH has taken the opportunity to introduce other editorial changes to the Product Information. In addition, a new RMP version 16.0 has also been approved based on the results of the study 109MS402 and the MAH proposed to remove pregnancy outcome as important potential risk. Moreover, the following changes have been also introduced • The due date of study 109MS401 has been revised from Q4-2024 to Q4-2023 • The requirement for submitting the Annual Progress Report for study 109MS401 in 2023 has been removed due to the outcome of procedure MEA 007.6 • The requirement to submit the interim study report of 109MS306 Part 2 has been removed being submitted in December 2022 (EMEA/H/C/002601/MEA/022)	26/10/2023		SmPC and PL	Section 4.6 of the SmPC has been amended in order to update information on pregnancy based on results from Tecfidera (dimethyl fumarate) Pregnancy Exposure Registry (TecGistry), an observational study aimed to address the safety concern of effects on pregnancy outcome and that prospectively evaluates pregnancy outcomes in women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product. The Package Leaflet is updated accordingly, and other editorial changes to the Product Information have been introduced. In addition, a new RMP version 16.0 has also been approved. For more information, please refer to the Summary of Product Characteristics.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
R/0083	Renewal of the marketing authorisation.	20/07/2023	15/09/2023	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of TECFIDERA in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0081	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	06/01/2023	n/a		
IB/0080	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/11/2022	n/a		
IA/0079	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	05/08/2022	n/a		
II/0078	Submission of the final report from study 109MS408; upon request by the PRAC as per final PSUR assessment report of procedure EMEA/H/C/PSUSA/00010143/20213. This is a Multicenter, Open-Label Study Evaluating the Effectiveness of Oral Tecfidera (Dimethyl Fumarate)	14/07/2022	n/a		

	on Multiple Sclerosis Disease Activity and Progression as well as on Patient-Reported Outcomes in Subjects with Relapsing Remitting Multiple Sclerosis in the Real-World Setting (PROTEC). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0073	C.I.6 (Extension of indication) type II Art.29 Extension of indication to include treatment of relapsing remitting multiple sclerosis (RRMS) in paediatrics patients from 13 years of age and over; as a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.3 and 6.6 of the Summary of Product Characteristics are updated. The Package Leaflet is updated accordingly. The risk management plan (RMP) is updated to version 13 based on Study 109MS306 data supporting the request for a paediatric indication. The marketing authorisation holder took the opportunity to update the RMP with the most updated data (Part II modules SIV, SV and SVII). The MAH applied for an extension of the marketing protection of one additional year in accordance with Article 14(11) of Regulation (EC) No 726/2004. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/04/2022	13/05/2022	SmPC and PL	Please refer to Scientific Discussion.

IB/0077	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/04/2022	n/a		
II/0069/G	This was an application for a group of variations. C.I.4 type II variation: Update of section 4.8 of the SmPC in order to add rhinorrhoea to the list of adverse drug reactions (ADRs) with frequency unknown based on a systematic review of information from clinical and non-clinical studies, post-marketing data and scientific literature. The Package Leaflet has been updated accordingly. C.I.4 type II variation: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study 109MS303 (ENDORSE) listed as a category 3 study in the RMP. This is a dose-blind, multicenter, extension study to determine the long-term safety and efficacy of two doses of BG00012 monotherapy in subjects with Relapsing-Remitting Multiple Sclerosis. The RMP version 12 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/01/2022	13/05/2022	SmPC and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No' Section 4.4 Blood/laboratory tests has been updated to inform that Lymphocyte counts should be followed until recovery (section 5.1). Upon recovery and in the absence of alternative treatment options, decisions about whether or not to restart Tecfidera after treatment discontinuation should be based on clinical judgement. In section 4.8, the number of exposed subjects (PY) and the periods of exposure have been updated; rhinorrhoea has been added to the list of adverse drug reactions (ADRs) with frequency unknown and subsections Hepatic function, lymphopenia, Infections, including PML and opportunistic infections based on final results from ENDORSE study. Section 5.1 pharmacodynamic effects subsection has been updated to inform about the dynamics of lymphocyte counts after discontinuation of Tecfidera therapy and to summarize the efficacy results from ENDORSE study. For more information, please refer to the Summary of Product Characteristics.

PSUSA/10143 /202103	Periodic Safety Update EU Single assessment - dimethyl fumarate, diroximel fumarate (multiple sclerosis)	11/11/2021	06/01/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10143/202103.
IA/0076/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	05/10/2021	n/a		
IAIN/0072/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	10/02/2021	06/01/2022	Annex II and PL	

	(excluding manufacturer for batch release) B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IA/0071/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	13/01/2021	n/a		
II/0063	Update of sections 4.3, 4.4 and 4.8 of the SmPC to reflect new available information on Progressive Multifocal Leukoencephalopathy (PML) risk monitoring based on a cumulative review of PML in the setting of mild lymphopenia. The Package Leaflet is updated accordingly. Additionally, the Product Information has been updated in line with QRD template (version 10.1). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/10/2020	24/11/2020	SmPC and PL	The PI has been updated to reflect new information available on Progressive Multifocal Leukoencephalopathy (PML) risk monitoring. The SmPC section 4.3 has been updated to reflect that Tecfidera is now contraindicated in patients with suspected or confirmed PML. The SmPC section 4.4 has been updated to reflect that Tecfidera should not be initiated in patients with severe lymphopenia (lymphocyte counts < 0.5 x 109/L) and that Tecfidera should be discontinued in patients with severe lymphopenia persisting for more than 6 months. The SmPC section 4.4 has also been updated to inform that PML cases

					have occurred in the setting of lymphopenia (lymphocyte counts below lower limit of normal as defined by local laboratory reference range) and to recommend enhanced vigilance in patients with lymphopenia taking into consideration additional factors that may contribute to an increased risk for PML in the setting of lymphopenia including duration of Tecfidera therapy (1-5 years), profound decreases in CD4+ and specially CD8+ T cell counts and prior immunosuppressive or immunomodulatory therapy. This section has been updated to inform that Tecfidera must be permanently discontinued if a patient develops PML The SmPC section 4.8 has been updated with additional findings on lymphocyte counts including CD4+ and CD8+ T cells counts in patients treated with Tecfidera with and without PML and new information on PML cases in patients treated with Tecfidera. The PL have been updated accordingly.
IA/0070	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	20/11/2020	n/a		
IA/0068	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/10/2020	n/a		
IA/0067/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or	08/09/2020	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
N/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/08/2020	24/11/2020	PL	
IA/0065	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	31/01/2020	n/a		

II/0058	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/01/2020	n/a		
PSUSA/10143 /201903	Periodic Safety Update EU Single assessment - dimethyl fumarate, diroximel fumarate (multiple sclerosis)	14/11/2019	09/01/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10143/201903.
II/0062	Update of sections 4.4 and 4.8 of the SmPC to add a warning on the newly identified the risk of herpes zoster and to add the adverse reaction herpes zoster with a frequency not known. The update is based on cumulative review data submitted in PSUSA/00010143/201903. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/11/2019	09/01/2020	SmPC and PL	The SmPC section 4.4 has been updated as follows: Herpes zoster infections Cases of herpes zoster have occurred with Tecfidera. The majority of cases were non-serious, however, serious cases, including disseminated herpes zoster, herpes zoster ophthalmicus, herpes zoster oticus, herpes zoster infection neurological, herpes zoster meningoencephalitis and herpes zoster meningomyelitis have been reported. These events may occur at any time during treatment. Monitor patients taking Tecfidera for signs and symptoms of herpes zoster especially when concurrent lymphocytopenia is reported. If herpes zoster occurs, appropriate treatment for herpes zoster should be administered. Consider withholding Tecfidera treatment in patients with serious infections until the infection has resolved (see section 4.8). The SmPC section 4.8 has been updated as follows: - to add the adverse reaction herpes zoster with a frequency not known. Infections

					Herpes zoster infections have been reported with Tecfidera use. In an ongoing long-term extension study, in which 1736 MS patients are treated with Tecfidera, approximately 5% experienced one or more events of herpes zoster, the majority of which were mild to moderate in severity. Most subjects, including those who experienced a serious herpes zoster infection, had lymphocyte counts above the lower limit of normal. Grade 2 and 3 lymphopenia prevailed in subjects with concurrent lymphocytopenia. In the post-marketing setting most cases of herpes zoster infection were non-serious and resolved with treatment. Limited data is available on ALC in patients with herpes zoster infection in the post-marketing setting. However, when reported, most patients experienced grade 2 (< 0.8 × 109/L to 0.5 × 109/L) or grade 3 (<0.5 × 109/L to 0.2 × 109/L) lymphopenia (see section 4.4). The PL have been updated accordingly.
IA/0064/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved	08/11/2019	n/a		

	stability protocol				
II/0061/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/09/2019	n/a		
II/0059	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/07/2019	14/11/2019	SmPC and PL	
IA/0057	A.6 - Administrative change - Change in ATC	29/03/2019	14/11/2019	SmPC	

	Code/ATC Vet Code				
II/0054/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/02/2019	n/a		
IAIN/0056	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2018	14/11/2019	SmPC and PL	
T/0055	Transfer of Marketing Authorisation	25/09/2018	14/11/2018	SmPC, Labelling and PL	
R/0053	Renewal of the marketing authorisation.	26/07/2018	20/09/2018	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of TECFIDERA in the approved indication remains favourable, but recommended that one additional five-year renewal be required based on the following pharmacovigilance grounds: Further characterisation of the important identified risks "decrease in leukocyte and lymphocyte counts" and "progressive multifocal leukoencephalopathy" (PML) is required. Safety studies to further characterise the risk of PML are currently still ongoing. The impact of PML on the

					benefit/risk balance can currently not be sufficiently assessed. Moreover, a high number of cases of herpes zoster have been reported. A potential association of this risk with decreases in lymphocyte counts caused by Tecfidera can still not be fully confirmed or excluded based on current data.
II/0051/G	This was an application for a group of variations. Submission of the final report from study 109HV114. This is a randomised, open-label, single-dose, crossover study in healthy volunteers to assess the pharmacokinetics of 4 new formulations compared to Tecfidera 240mg capsules. Submission of the final report from study 109MS201 listed as a category 3 study in the RMP. This is an open-label, multicentre study in patients with Relapsing-Remitting Multiple Sclerosis to evaluate the safety and tolerability of 240 mg Tecfidera three times daily administered as add-on therapy to beta interferons (IFNβ) or Glatiramer Acetate (GA). Submission of the synopsis report from study 109MS308. This is a randomised, multicentre, double-blind, placebo-controlled study of the efficacy and safety of Tecfidera in delaying disability progression in patients with secondary progressive multiple sclerosis. Submission of the final report (abbreviated) from study 109MS416. This is a randomised, multicentre,	17/05/2018	n/a		

	treatment-blinded, parallel group Phase IIIb study aimed to evaluate the effect of 6-week up-titration of Tecfidera treatment on the severity of gastrointestinal adverse effects in patients with multiple sclerosis. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0052	A.7 - Administrative change - Deletion of manufacturing sites	09/04/2018	n/a		
II/0050	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/02/2018	n/a		
II/0041	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2018	28/05/2018	SmPC, Labelling and PL	Cases of anaphylaxis/anaphylactoid reaction have been reported following Tecfidera administration in the post-marketing setting. Symptoms may include dyspnoea, hypoxia, hypotension, angioedema, rash or urticaria. The mechanism of dimethyl fumarate induced anaphylaxis is

					unknown. Reactions generally occur after the first dose, but may also occur at any time during treatment, and may be serious and life threatening. Patients should be instructed to discontinue Tecfidera and seek immediate medical care if they experience signs or symptoms of anaphylaxis. Treatment should not be restarted.
II/0037	Submission of a Clinical Study Report for study 109MS307: An Open-Label Study to Assess the Immune Response to Vaccination in Tecfidera-Treated Versus Interferon-Treated Subjects With Relapsing Forms of Multiple Sclerosis. This variation includes an update to section 4.5 (Interaction with other medicinal products and other forms of interaction) of the Summary of Product Characteristics (SmPC) and section 2 of the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2018	28/05/2018	SmPC and PL	Concomitant administration of non-live vaccines during Tecfidera therapy has been studied in study 109MS307. In this clinical study which involved a total of 71 patients with relapsing remitting multiple sclerosis, patients on Tecfidera 240 mg twice daily for at least 6 months (n=38) or non-pegylated interferon for at least 3 months (n=33), mounted a comparable immune response (defined as ≥2-fold increase from pre- to post-vaccination titer) to tetanus toxoid (recall antigen) and a conjugated meningococcal C polysaccharide vaccine (neoantigen), while the immune response to different serotypes of an unconjugated 23-valent pneumococcal polysaccharide vaccine (T-cell independent antigen) varied in both treatment groups. A positive immune response defined as a ≥4 -fold increase in antibody titer to the three vaccines, was achieved by fewer subjects 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. No clinical data are available on the efficacy and safety of live attenuated vaccines in patients taking Tecfidera.
II/0049	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/02/2018	n/a		

II/0045	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/02/2018	n/a		
II/0036/G	This was an application for a group of variations. Submission of two Clinical Study Reports: 1) Clinical Study Report for study 109HV321: A Randomized, Double-Blind, Phase 3b Study to Evaluate the Safety and Tolerability of Tecfidera when Administered as 240 mg BID (twice daily) Dose Regimen with and Without Aspirin Compared to Placebo or Following a Slow Titration. 2) Clinical Study Report for study 109MS406 (ASSURE): A Phase 4, Randomized, Double-Blind Study with a Safety Extension Period to Evaluate the Effect of Aspirin on Flushing Events in Subjects with Relapsing-Remitting Multiple Sclerosis Treated with Tecfidera (Dimethyl Fumarate) Delayed-release Capsules. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/02/2018	28/05/2018	SmPC	

IAIN/0048/G	This was an application for a group of variations. B.III.1.b.1 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for an AS from a new or an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)	17/11/2017	n/a		
II/0042	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2017	28/05/2018	SmPC	
PSUSA/10143 /201703	Periodic Safety Update EU Single assessment - dimethyl fumarate, diroximel fumarate (multiple sclerosis)	26/10/2017	n/a		PRAC Recommendation - maintenance

IB/0046	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/09/2017	n/a		
II/0044	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/09/2017	n/a		
II/0043/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/09/2017	n/a		
IA/0047	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/09/2017	n/a		
II/0035	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/05/2017	28/05/2018	SmPC and PL	
IB/0039	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/04/2017	n/a		
IA/0038/G	This was an application for a group of variations.	07/04/2017	n/a		

	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0034	To update Section 5.3 (Preclinical Safety Data) of the Summary of Product Characteristics (SmPC). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/11/2016	12/04/2017	SmPC	
PSUSA/10143 /201603	Periodic Safety Update EU Single assessment - dimethyl fumarate, diroximel fumarate (multiple sclerosis)	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0026	Submission of a new RMP Version 7.1 following the outcome of the evaluation from CHMP procedure WS/689 related to lymphopenia and progressive multifocal leukoencephalopathy (PML). As requested in conclusion of WS/689, a discussion on the totality of the nonclinical and clinical work being undertaken to further understand the lymphopenia with Tecfidera treatment was submitted. The MAH also took the opportunity to reformat the RMP in line with the	15/09/2016	n/a		

	current RMP template. Finally, the draft protocol for the category 3 PASS study 109MS419 (a retrospective, multicentre, observational study to assess the effect of Tecfidera delayed-release capsules on lymphocyte subsets in subjects with relapsing forms of multiple sclerosis) was also submitted. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
II/0024/G	This was an application for a group of variations. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.f.1.e - Stability of FP - Change to an approved stability protocol	15/09/2016	n/a		

	B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0030	Update of sections 4.4 and 4.8 of the SmPC to reflect the occurrence of Progressive Multifocal Leukoencephalopathy (PML) in the presence of moderate (in addition to severe) prolonged lymphopenia. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/07/2016	12/04/2017	SmPC and PL	In clinical studies (both controlled and uncontrolled), 9% of patients had lymphocyte counts ≥0.5 x 109/L and <0.8 x 109/L for at least six months (moderate prolonged lymphopenia). If therapy is continued in the presence of moderate to severe prolonged lymphopenia, the risk of an opportunistic infection, including Progressive Multifocal Leukoencephalopathy (PML), cannot be ruled out. At the first sign or symptom suggestive of PML, withhold Tecfidera and perform appropriate diagnostic evaluations. The symptoms of PML may be similar to an MS relapse. 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. The benefit/risk should be assessed in patients with lymphocyte counts ≥0.5 x 109/L and <0.8 x 109/L for more than six months.
II/0028	Update of section 4.5 of the SmPC based on the results of study 109HV113, conducted to investigate the effects of Tecfidera on the PK of a commonly used oral contraceptive in healthy females of childbearing potential. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in Romania and Norway in the Package Leaflet.	14/07/2016	12/04/2017	SmPC and PL	In an in vivo study, co-administration of Tecfidera with a combined oral contraceptives (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 Tecfidera on their exposure is not expected.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0025	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/06/2016	n/a		
IAIN/0032/G	This was an application for a group of variations. B.III.1.b.1 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for an AS from a new or an already approved manufacturer B.III.1.b.1 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for an AS from a new or an already approved manufacturer B.III.1.b.1 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for an AS from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)	08/06/2016	n/a		

II/0029	Update of section 4.9 of the SmPC to reflect cases of overdose that have been observed with Tecfidera. The Package Leaflet has been updated accordingly. In addition, the MAH has taken the opportunity to update the contact details of the local representatives for Estonia and Latvia in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/06/2016	12/04/2017	SmPC and PL	Cases of overdose with Tecfidera have been reported. The symptoms described in these cases were consistent with the known adverse event profile of Tecfidera. There are no known therapeutic interventions to enhance elimination of Tecfidera nor is there a known antidote. In the event of overdose, it is recommended that symptomatic supportive treatment be initiated as clinically indicated.
IB/0031	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	18/05/2016	12/04/2017	SmPC	
IB/0027/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	22/03/2016	n/a		
II/0022	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	11/02/2016	n/a		

WS/0689/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/11/2015	16/12/2015	SmPC and Labelling	
IA/0021	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	14/12/2015	n/a		
IAIN/0023	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	10/12/2015	n/a		
PSUSA/10143 /201503	Periodic Safety Update EU Single assessment - dimethyl fumarate, diroximel fumarate (multiple sclerosis)	08/10/2015	n/a		PRAC Recommendation - maintenance
IB/0019/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	05/10/2015	n/a		

	Replacement/addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IG/0615	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	11/09/2015	n/a		
IB/0018	A.3 - Administrative change - Change in name of the AS or of an excipient	22/07/2015	16/12/2015	SmPC and PL	
IB/0016/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	26/06/2015	n/a		

IAIN/0015	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	17/06/2015	16/12/2015	Annex II and PL	
IB/0014/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.c.3.c - Change in test procedure for the immediate packaging of the AS - Deletion of a test	22/04/2015	n/a		

	procedure if an alternative test procedure is already authorised				
IB/0013	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	27/03/2015	n/a		
IB/0012	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	05/03/2015	n/a		
IA/0010	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	09/12/2014	n/a		
IA/0009/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	05/12/2014	n/a		

	procedure				
IB/0008	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	28/10/2014	13/04/2015	SmPC, Labelling and PL	
PSUV/0005	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IA/0007	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	25/09/2014	n/a		
IAIN/0006/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place A.7 - Administrative change - Deletion of manufacturing sites A.5.b - Administrative change - Change in the name	20/06/2014	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IG/0431	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/04/2014	n/a		
IB/0002/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.e.7.b - Change in supplier of packaging	09/04/2014	13/04/2015	SmPC	

	components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				