Dificlir

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
IA/0055	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	05/08/2024	n/a		
IB/0054/G	This was an application for a group of variations.	28/06/2024	n/a		

[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).

	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				
IB/0053	B.I.z - Quality change - Active substance - Other variation	20/06/2024	n/a		
PSUSA/1390/ 202305	Periodic Safety Update EU Single assessment - fidaxomicin	11/01/2024	n/a		PRAC Recommendation - maintenance
IB/0052/G	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	15/11/2023	01/12/2023	SmPC, Labelling and PL	
II/0049	Update of section 4.2 and 5.1 of the SmPC in order to introduce information a new posology regimen based on final results from EXTEND study - A Phase IIIb/IV Randomized, Controlled, Open-Label, Parallel Group Study to Compare the Efficacy of Vancomycin Therapy to Extended Duration Fidaxomicin Therapy in the Sustained Clinical Cure of Clostridium difficile Infection in an Older Population. 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	10/11/2022	12/12/2022	SmPC and PL	Based on the EXTEND study, a phase 3b/4 study that evaluated the efficacy of Extended pulsed fidaxomicin (EPFX) in the treatment of Clostridioides difficile infections (CDI) in male and female patients aged 60 years and older compared with standard vancomycin therapy, language on extended pulse dosing regimen (200 mg (one tablet) administered twice daily (once every 12 hours) for 5 days, and then every other day for a further 20 days (10 tablets) was introduced in Section 4.2 and 5.1 of the SmPC and section 3 of the Dificlir PL. For more information, please refer to the Summary of

	data				Product Characteristics.
IB/0050/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	14/10/2022	n/a		
IAIN/0048	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	07/03/2022	24/06/2022	Annex II and PL	
IB/0046	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	11/10/2021	n/a		
IAIN/0045/G	This was an application for a group of variations. Replacement or addition of a manufacturer responsible for importation and/or batch release.	19/05/2021	24/06/2022	Annex II and PL	

	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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 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.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				
T/0044	Transfer of Marketing Authorisation	12/02/2021	09/03/2021	SmPC, Labelling and PL	
PSUSA/1390/202005	Periodic Safety Update EU Single assessment - fidaxomicin	14/01/2021	n/a		PRAC Recommendation - maintenance
IA/0043/G	This was an application for a group of variations.	09/12/2020	n/a		

	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 procedure				
IA/0042	B.I.c.z - Container closure system of the AS - Other variation	09/12/2020	n/a		
IAIN/0041/G	This was an application for a group of variations. B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/11/2020	09/03/2021	Annex II and PL	
IA/0039	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	07/08/2020	n/a		

	manufacturer of a novel excipient				
IA/0038/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.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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)	29/06/2020	n/a		
X/0034/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form	12/12/2019	13/02/2020	SmPC, Annex II, Labelling and PL	
IA/0037/G	This was an application for a group of variations.	05/12/2019	n/a		

	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.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.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) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0036/G	This was an application for a group of variations. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	08/05/2019	n/a		
IA/0035	A.7 - Administrative change - Deletion of manufacturing sites	23/04/2019	n/a		
II/0033	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	31/10/2018	n/a		

	by new additional data to be submitted by the MAH where significant assessment is required				
II/0032/G	This was an application for a group of variations. Update of sections 4.4 and 5.2 of the SmPC in order to update the safety information based on results from the PROFILE study, an open label study designed to evaluate the pharmacokinetics of fidaxomicin in IBD subjects with CD. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 9.0 has also been 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/05/2018	19/07/2018	SmPC and PL	The warning section of the SmPC is updated to reflect that there is data available on patients with concomitant inflammatory bowel disease (IBD). These data indicates no major difference in plasma concentrations of fidaxomicin or its main metabolite in patients with IBD as compared with patients without IBD in other studies. The maximum fidaxomicin levels in CDI patients with concomitant IBD were within the range of levels found in CDI patients without IBD.
PSUSA/1390/ 201705	Periodic Safety Update EU Single assessment - fidaxomicin	11/01/2018	n/a		PRAC Recommendation - maintenance
IA/0030	B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging	03/08/2017	19/07/2018	SmPC, Labelling and	

	container without a complete deletion of a strength or pharmaceutical form			PL	
II/0028	C.I.11: Updated RMP version 8 in order to remove the post-authorization measure (PAM) MEA003 (concerning clinical study 2819-CL-2001 in patients with Clostridium difficile Infection who will receive a second course of fidaxomicin) due to the non-feasibility of the study. 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	20/07/2017	n/a		The limited feasibility to perform the MEA 003 and also to retrospectively collect data from patients with at least two courses of fidaxomicin it is acknowledged. It is also considered appropriate to conclude the ClosER study as planned. The updated RMP version 8 was approved.
IB/0029/G	This was an application for a group of variations. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	26/04/2017	n/a		
PSUSA/1390/ 201605	Periodic Safety Update EU Single assessment - fidaxomicin	12/01/2017	n/a		PRAC Recommendation - maintenance
R/0026	Renewal of the marketing authorisation.	23/06/2016	22/08/2016	SmPC, Annex II, Labelling	

				and PL	
IA/0025	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	09/12/2015	n/a		
PSUSA/1390/ 201505	Periodic Safety Update EU Single assessment - fidaxomicin	03/12/2015	n/a		PRAC Recommendation - maintenance
II/0022	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	25/06/2015	n/a		
PSUSA/1390/ 201411	Periodic Safety Update EU Single assessment - fidaxomicin	11/06/2015	n/a		PRAC Recommendation - maintenance
II/0021	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	26/02/2015	n/a		
PSUV/0020	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
II/0016	Update of of sections 4.5 and 5.2 of the SmPC with the results from study 2819-CL-2003, assessing the effect of multiple doses of fidaxomicin on the pharmacokinetics of a single dose of rosuvastatin in healthy male subjects. In addition, the local representatives for Estonia, Lithuania and Latvia are updated in the PL.	26/06/2014	28/05/2015	SmPC and PL	The potential drug drug interaction between fidaxomicin and rosuvastatin was investigated in study 2819-CL-2003, an open-label, randomized, two-way crossover study in healthy male subjects following multiple oral doses of fidaxomicin and a single oral dose of rosuvastatin. The study demonstrated that fidaxomicin does not have a clinically significant effect on the exposure of rosuvastatin. The Sections 4.5 and 5.2 of the SmPC were updated in line

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				with these results. The RMP was updated accordingly. The CHMP concluded that these results do not affect the overall benefit/risk balance for Dificlir, which remains positive.
IA/0019/G	This was an application for a group of variations. 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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - 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	20/06/2014	n/a		
PSUV/0017	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance
PSUV/0015	Periodic Safety Update	23/01/2014	21/03/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0015.
IAIN/0018	C.I.8.a - Introduction of or changes to a summary of	12/03/2014	n/a		

	Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location				
IAIN/0014/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the PhV system	25/09/2013	n/a		
IA/0013	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits	19/07/2013	n/a		
II/0011	Update of sections 4.4 and 4.8 of the SmPC to add a warning on angioedema and hypersensitivity reactions and further to update the SmPC section 5.2 to include the in vitro data obtained with regard to fidaxomicin and inhibition of OATP2B1, BCRP and MRP2. In addition, section 4.5 of the SmPC is amended, in order to improve readability. The Package Leaflet is updated accordingly. The list of local representatives is updated, to add a representative for Croatia. Furthermore, the PI is being brought in line with the latest QRD template version 9 (and black symbol information requirement is implemented).	27/06/2013	13/12/2013	SmPC, Annex II and PL	Review of the Phase 3 clinical trial database revealed no significant hypersensitivity reactions that were believed to be related to fidaxomicin. Skin rash was infrequent (2.8%). From the date of first marketing in the U.S., fidaxomicin received five non-serious, medically confirmed reports of potential hypersensitivity reactions (four reports of rash and one report of a burning sensation of the throat, arms, and legs). All reported symptoms were mild and either self-limiting or easily managed with anti-histamines. Hence, the post-marketing database was searched for any events equal to Anaphylactic reaction (SMQ) or Angioedema (SMQ). Two such cases were identified during

	The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				this reporting period of which one had a positive rechallenge reported. Based on aforementioned information, following assessment of PSUR 1 (covering period 27/11/2011-26/05/2012), the MAH had been requested to add appropriate warnings and precautions to the SmPC. In addition, as part of Post-Authorisation Measures, two in vitro studies showed that neither fidaxomicin nor OP-1118 are substrates, but both are inhibitors, of transporters BCRP, MRP2, and OATP2B1. A clinical study is planned to evaluate the clinical relevance of these in vitro data. In the meantime, an appropriate statement is introduced in section 5.2 of the SmPC.
IAIN/0012/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	06/05/2013	n/a		
IAIN/0010	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	18/03/2013	n/a		
IAIN/0009/G	This was an application for a group of variations.	08/02/2013	n/a		

	C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IAIN/0008/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	11/01/2013	13/12/2013	SmPC, Annex II, Labelling and PL	
IB/0007	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)	17/12/2012	13/12/2013	SmPC	
IA/0006/G	This was an application for a group of variations. 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 currently approved batch size 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.a - Change to in-process tests or limits applied during the manufacture of the AS -	10/12/2012	n/a		

	Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits				
IAIN/0005	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	26/10/2012	n/a		
IAIN/0004/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	12/06/2012	29/10/2012	Annex II and PL	
IAIN/0003/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.b.2 - Change to batch release arrangements	04/04/2012	27/06/2012	SmPC	

	and quality control testing of the FP - Including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites A.6 - Administrative change - Change in ATC Code/ATC Vet Code B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
IB/0002/G	This was an application for a group of variations. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	23/03/2012	n/a		
T/0001	Transfer of Marketing Authorisation	11/01/2012	06/02/2012	SmPC and PL	