Firdapse

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
S/0071	Annual re-assessment.	22/07/2021	n/a		
S/0066	10th annual re-assessment.	17/09/2020	18/11/2020	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation

[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).

					of Firdapse should be maintained. It is proposed a new SOB that the MAH shall provide yearly updates (simultaneously with submission of Periodic Safety Update reports) on any new information concerning efficacy and safety of the product in patients with LEMS in order to address the remaining uncertainties especially related to the need to for additional treatment when Firdapse treatment can no longer control symptoms of LEMS.
IAIN/0070/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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	02/09/2020	18/11/2020	SmPC, Annex II and PL	
IA/0069	A.7 - Administrative change - Deletion of manufacturing sites	21/08/2020	n/a		
T/0068	Transfer of Marketing Authorisation	28/04/2020	14/05/2020	SmPC, Labelling and	

				PL	
IA/0067/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	17/03/2020	n/a		
R/0062	Renewal of the marketing authorisation.	27/06/2019	23/08/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Firdapse in the approved indication remains favourable. The LEMS Registry study (LEMS-01) is ongoing. Updates to the Product Information were made in line with the SmPC guideline and the latest QRD template.
PSUSA/141/201812	Periodic Safety Update EU Single assessment - amifampridine	11/07/2019	n/a		PRAC Recommendation - maintenance
IB/0065/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.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	05/07/2019	n/a		

S/0064	9th annual re-assessment	27/06/2019	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Firdapse should be maintained.
II/0060	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/05/2019	23/08/2019	SmPC	
II/0061	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/01/2019	n/a		
IB/0058/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	07/09/2018	n/a		
S/0053	Annual re-assessment.	26/07/2018	n/a		
T/0057	Transfer of Marketing Authorisation	14/06/2018	13/07/2018	SmPC, Labelling and	

				PL	
PSUSA/141/201712	Periodic Safety Update EU Single assessment - amifampridine	12/07/2018	n/a		PRAC Recommendation - maintenance
IB/0055	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	21/03/2018	n/a		
IB/0054	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	21/03/2018	n/a		
IB/0052/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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	19/10/2017	n/a		

	corresponding test method B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
S/0049	Annual re-assessment.	14/09/2017	n/a		
PSUSA/141/201612	Periodic Safety Update EU Single assessment - amifampridine	06/07/2017	n/a		PRAC Recommendation - maintenance
IA/0051	A.7 - Administrative change - Deletion of manufacturing sites	18/04/2017	30/10/2017	Annex II and PL	
II/0043	Update of sections 4.4 and 5.3 of the SmPC for Firdapse in order to update the warning regarding carcinogenicity risk and to provide the findings from	23/03/2017	30/10/2017	SmPC and Annex II	In fulfilment of SOB 004 (specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances), the

	the carcinogenicity reports from studies BNM125-13-026 and BMN125-13-011. Annex II is updated to reflect the fulfilment of the specific obligation following the submission of the two non-clinical studies. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Marketing Authorisation Holder has submitted the final results of BMN125-13-011andBNM125-13-026 .The purpose of study BMN125-13-011 was to evaluate the palatability and determine the toxicokinetics of Firdapse phosphate when offered in the diet. The results were used to determine the initial dietary dose levels for the carcinogenicity study BMN125-13 026. In the 2-year rat dietary carcinogenicity study BMN125-13 026, amifampridine caused small but statistically significant dose-related increases in the incidence of Schwannomas in both genders and of endometrial carcinomas in females. Amifampridine was not genotoxic in a standard battery of in vitro and in vivo tests. The correlation between the use of amifampridine and the development of tumours in humans is unknown at this time.Most Schwannomas are benign and asymptomatic. They can present in many locations, therefore the clinical presentation can be varied. A diagnosis of Schwannoma should be considered for patients who present with symptoms such as a mass that is painful on palpation or symptoms similar to a compressive neuropathy. Schwannomas are generally slow-growing and can exist for months to years without producing symptoms. The benefit of continuing treatment with amifampridine should be reviewed for any patient who develops a Schwannoma. Amifampridine should be used with caution in patients with an increased risk of Schwannomas, such as patients with past medical history of such tumours, neurofibromatosis Type 2 or schwannomatosis.
IB/0048	Change in the UV assay test method for assessing Potency of Firdapse tablets for release and stability testing. In addition, the MAH took the opportunity to	06/02/2017	n/a		

	submit an editorial change to correct an error in the quantity of tablets used as samples for the mass uniformity test method. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation				
IB/0047/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.z - Change in control of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	20/12/2016	n/a		
IAIN/0045	A.5.a - Administrative change - Change in the name	11/11/2016	30/10/2017	Annex II and	

	and/or address of a manufacturer/importer responsible for batch release			PL	
II/0042	Submission of the clinical study report LMS-002 to support the efficacy of Firdapse in patient with Lambert-Eaton myasthenic syndrome (LEMS). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2016	n/a		
IB/0044	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	07/10/2016	n/a		
II/0038	Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update the safety information with data from the final CSR of study REN-002 on renal impairment. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. Moreover, the MAH took the opportunity to make correction in section 5.3 of the SmPC. The RMP version 8.0 has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2016	29/07/2016	SmPC and PL	
PSUSA/141/2	Periodic Safety Update EU Single assessment -	07/07/2016	n/a		PRAC Recommendation - maintenance

01512	amifampridine				
S/0040	6th Annual Re-assessment	23/06/2016	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Firdapse should be maintained.
IG/0658	A.1 - Administrative change - Change in the name and/or address of the MAH	02/02/2016	29/07/2016	SmPC, Labelling and PL	
S/0036	5th Annual Re-assessment.	24/09/2015	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Firdapse should be maintained.
PSUSA/141/201412	Periodic Safety Update EU Single assessment - amifampridine	09/07/2015	n/a		PRAC Recommendation - maintenance
II/0033/G	This was an application for a group of variations. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions 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	21/05/2015	n/a		

II/0034	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	26/03/2015	n/a		
IAIN/0035	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	13/02/2015	24/02/2016	Annex II and PL	
R/0029	Renewal of the marketing authorisation.	25/09/2014	28/11/2014	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considered that the risk-benefit balance of Firdapse in the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults remains favourable and therefore recommended the renewal of the marketing authorisation. In addition, the SmPC was updated in sections 4.6 and 5.3 in order to reflect to reflect newly available pre-clinical data regarding developmental and reproductive toxicity. The Package Leaflet (PL) was updated accordingly. Considering that Firdapse was authorised under exceptional circumstances and two safety related specific obligations were still outstanding at the time of this renewal, i.e. the LEMS registry and carcinogenicity testing, as well as taking into account the overall limitations in patient exposure to Firdapse, the CHMP was of the view that one additional five-year renewal on the basis of pharmacovigilance grounds was required.
S/0027	4th Annual Re-assessment	20/11/2014	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data

					submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Firdapse should be maintained.
IA/0032/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	06/10/2014	n/a		
IG/0471	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	04/08/2014	n/a		
PSUV/0028	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
II/0026	Update of the following sections of the SmPC based on data from a completed QTc study (specific obligation): 4.4 to add a statement providing information on the absence of ECG morphological changes, 4.8 to include additional terms with > 10% incidence (hypoaesthesia, hypoaesthesia oral paraesthesia oral, hyperhidrosis and cold sweat) and 4.9 to reflect the experience with higher doses	20/03/2014	28/11/2014	SmPC, Annex II, Labelling and PL	Following completion of a QTc study, the Product Information was updated to add new information regarding cardiac safety. Specifically, the CHMP considered that no clinically relevant ECG morphological changes were observed in healthy volunteers after administration of amifampridine phosphate. The Product Information was also updated to include additional adverse reactions reported, i.e. reduced sense of touch or sensation and

	tested. In parallel, the MAH proposed to reflect results from the QTc study in section 5.1 of the SmPC. The Package Leaflet was updated in accordance. Furthermore, consequently to the submission of the final study report of this QTc study, the respective specific obligation was deleted from Annex II. In addition, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				increased sweating/cold sweat. Furthermore, vomiting and abdominal pain were reinforced as symptoms that the patient may experience, if overdosed. With completion of the QTc study and submission of its results, the CHMP agreed that the respective specific obligation has been fulfilled.
S/0022	3rd Annual Re-assessment	21/11/2013	16/01/2014	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Firdapse should be varied.
IB/0025/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	17/12/2013	n/a		

	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.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.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0024/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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	13/08/2013	n/a		
IA/0023	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	04/06/2013	n/a		
S/0016	2nd Annual Re-assessment.	17/01/2013	13/03/2013	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal

					product, concluded that the benefit/risk balance for the product remained favourable.
IAIN/0021	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/02/2013	n/a		
IG/0207	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	03/08/2012	n/a		
IB/0019/G	This was an application for a group of variations. B.II.a.2.b - Change in the shape or dimensions of the pharmaceutical form - Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses 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.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 batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.b.2 - Change to batch release arrangements	02/08/2012	29/10/2012	Annex II and PL	

	and quality control testing of the FP - Including batch control/testing B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
IG/0177	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	25/05/2012	n/a		
IA/0017/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.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	19/04/2012	n/a		
IB/0015	Variation to introduce a new Detailed Description of	19/03/2012	n/a		

	the Pharmacovigilance System (DDPS) into Module 1.8.1 of the Firdapse dossier. This is a new pharmacovigilance system for Firdapse, but has already been assessed for another product of the same MAH (Naglazyme). 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				
S/0009	Annual Re-assessment	22/09/2011	21/11/2011	SmPC and Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
IB/0013	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	09/11/2011	n/a		
IB/0012	B.II.b.2.z - Change to batch release arrangements and quality control testing of the FP - Other variation	21/07/2011	n/a		
IA/0011	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	12/05/2011	n/a		
IB/0008	B.I.c.z - Container closure system of the AS - Other variation	06/04/2011	n/a		

IA/0010/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 responsible for batch release 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.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	06/04/2011	n/a	Annex II and PL	
II/0007/G	This was an application for a group of variations. Grouped application to implement changes relating to the manufacturing process of the active substance, including: - addition of an additional manufacturer of the active substance, - increase in the batch size of the active substance, - addition of an additional supplier of a starting material used in manufacturing process of the active substance, - change the quality release testing arrangement for the active substance. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions	17/02/2011	25/02/2011		

	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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
IA/0006	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	10/09/2010	n/a	Annex II and PL	
IA/0005	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/05/2010	n/a		
T/0004	Transfer of Marketing Authorisation	19/02/2010	15/04/2010	SmPC, Labelling and PL	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/02/2010	n/a	Labelling	
IA/0001	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	28/01/2010	n/a	SmPC, Annex II, Labelling and PL	