Tegsedi

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/0040	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	13/12/2023	n/a		
II/0038	Update of sections 4.4 and 4.8 of the SmPC in order to modify the warning on liver monitoring and drug-induced liver injury and to add 'drug-induced liver	30/11/2023		SmPC, Annex II and PL	Please refer to Scientific Discussion 'Tegsedi-H-C-004782-II-Var.38'.

[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).

	injury' to the list of adverse drug reactions (ADRs) with frequency not known, following the request in the Assessment Report for PAM procedure EMEA/H/C/004782/LEG/008. The Annex II and Package Leaflet are updated accordingly. The RMP version 4.2 has also been submitted. In addition, the MAH took the opportunity to introduce minor updates to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Amendments to the SmPC to modify the warning on liver monitoring and drug-induced liver injury and to add 'drug-induced liver injury' to the list of adverse drug reactions. Update of the risk management plan to include Hepatotoxicity as a new important identified risk. Additional Risk Minimization Measures (patient alert cards) are also updated accordingly. The Annex II and Package Leaflet are also updated and in addition, the MAH took the opportunity to introduce minor updates to the PI. For more information, please refer to the Summary of Product Characteristics.
IAIN/0037	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	10/07/2023	n/a		
PSUSA/10697 /202207	Periodic Safety Update EU Single assessment - inotersen	23/02/2023	19/04/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10697/202207.
R/0035	Renewal of the marketing authorisation.	26/01/2023	24/03/2023	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Tegsedi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0034	Submission of the final report from study ISIS 420915-CS3, listed as a category 3 in the RMP. This is an Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP).	09/03/2023	n/a		Submission of the final report from Open-Label Extension Study to Assess the Long-Term Safety and Efficacy in Patients with Familial Amyloid Polyneuropathy (FAP).

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IAIN/0036	A.1 - Administrative change - Change in the name and/or address of the MAH	07/11/2022	24/03/2023	SmPC, Labelling and PL	
IB/0031	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/10/2022	24/03/2023	Annex II	
IA/0033/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.II.d.2.a - Change in test procedure for the finished product - 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	19/09/2022	n/a		
IA/0030	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished	22/08/2022	n/a		

	product - Tightening of in-process limits				
IA/0029/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.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) 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	08/08/2022	n/a		
IB/0028	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)	28/07/2022	21/09/2022	SmPC	
IB/0027	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	27/07/2022	n/a		
II/0026	Updated RMP version 3.1 removes carcinogenicity in rats as missing information, adds a targeted questionnaire as routine pharmacovigilance measure	10/03/2022	n/a		

	and a patient alert card as additional risk minimisation for liver transplant rejection. Adds 'injection site reactions' and 'immunogenicity' as risks not considered important for inclusion in the summary of safety concerns (SVII.1.) and updates the patient alert card with additional warnings on hepatic monitoring and ocular toxicity. Further sections of the RMP are updated. 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				
PSUSA/10697 /202107	Periodic Safety Update EU Single assessment - inotersen	10/02/2022	n/a		PRAC Recommendation - maintenance
PSUSA/10697 /202101	Periodic Safety Update EU Single assessment - inotersen	16/09/2021	09/11/2021	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10697/202101.
IB/0024	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/10/2021	21/09/2022	SmPC, Annex II, Labelling and PL	
IB/0023	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)	19/07/2021	09/11/2021	SmPC, Labelling and PL	To extend the shelf life from 36 months to 48 months when stored at 2°-8°C and protected from light.
IB/0022	B.II.z - Quality change - Finished product - Other	30/06/2021	n/a		

	variation				
PSUSA/10697 /202007	Periodic Safety Update EU Single assessment - inotersen	25/02/2021	21/04/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10697/202007.
IB/0019	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/03/2021	n/a		
IA/0020	A.7 - Administrative change - Deletion of manufacturing sites	05/03/2021	n/a		
IB/0018	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	07/12/2020	n/a		
IA/0017	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	27/11/2020	n/a		
IAIN/0016/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.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	16/10/2020	n/a		

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
PSUSA/10697 /202001	Periodic Safety Update EU Single assessment - inotersen	03/09/2020	n/a		PRAC Recommendation - maintenance
II/0011	Update of SmPC section 5.3 to reflect the results of rat carcinogenicity study. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	03/09/2020	03/11/2020	SmPC and PL	The final report of a 2-year subcutaneous (s.c.) carcinogenicity study of ISIS 420915 has shown dose-related incidence of subcutaneous pleomorphic fibrosarcoma and subcutaneous fibrosarcoma (monomorphic type) at 2 and 6 mg/kg/week in the injection site or injection site regions. The human relevance of these findings is considered to be low.
IB/0014	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)	14/05/2020	03/11/2020	SmPC	
IB/0013/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	22/04/2020	n/a		

	specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
PSUSA/10697 /201907	Periodic Safety Update EU Single assessment - inotersen	16/01/2020	n/a		PRAC Recommendation - maintenance
IAIN/0010/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code 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.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.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	22/11/2019	03/11/2020	SmPC, Annex II and PL	
IB/0009/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of	24/10/2019	n/a		

	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				
PSUSA/10697 /201901	Periodic Safety Update EU Single assessment - inotersen	25/07/2019	19/09/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10697/201901.
IB/0007	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)	31/07/2019	n/a		
IA/0006/G	This was an application for a group of variations. 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) B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/06/2019	n/a		
IB/0005	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)	10/05/2019	19/09/2019	SmPC	

T/0003	Transfer of Marketing Authorisation	01/02/2019	01/03/2019	SmPC, Labelling and PL	
IB/0002	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	26/11/2018	n/a		
T/0001	Transfer of Marketing Authorisation	28/08/2018	12/09/2018	SmPC, Labelling and PL	