Evrysdi

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
PSUSA/10925 /202308	Periodic Safety Update EU Single assessment - risdiplam	07/03/2024	n/a		PRAC Recommendation - maintenance
II/0021	Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update efficacy and safety information based on primary analysis results from study	01/02/2024		SmPC and PL	For more information, please refer to the Summary of Product Characteristics.

[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).

	BN40703 (RAINBOWFISH); this is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in patients aged from birth to 6 weeks (at first dose) who are genetically diagnosed with SMA (SMN1 deletion and any SMN2 copies) but not yet presenting with symptoms. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the Instructions for Use. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0020	Submission of an updated RMP version 2.0 in order to remove the important potential risk of retinal toxicity with risdiplam due to the absence of evidence of retinal toxicity based on thorough ophthalmological monitoring in clinical studies to date. 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	11/01/2024	n/a		Not applicable
II/0018	Update of section 5.3 of the SmPC in order to update carcinogenicity information based on final results	07/12/2023		SmPC and PL	Section 5.3 of the SmPC has been updated in order to add carcinogenicity information based on final results from

	from study 8447237. This is a 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Wistar Rat to investigate the tumorigenic potential of Evrysdi. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				study 8447237. This is a 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Wistar Rat to investigate the tumorigenic potential of Evrysdi. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. For more information, please refer to the Summary of Product Characteristics.
II/0017	Update of section 5.1 of the SmPC in order to add information on cardiac electrophysiology based on final results from study BP42817 (QTc Study), listed as a category 3 PASS in the RMP. This is a Phase 1, double-blind, placebo and positive controlled crossover study to investigate the effects of risdiplam on QTc interval in healthy subjects. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/11/2023		SmPC	Section 5.1 of the SmPC has been updated in order to add information on cardiac electrophysiology based on final results from study BP42817 (QTc Study), listed as a category 3 PASS in the RMP. This is a Phase 1, double-blind, placebo and positive controlled crossover study to investigate the effects of risdiplam on QTc interval in healthy subjects. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10925 /202302	Periodic Safety Update EU Single assessment - risdiplam	31/08/2023	n/a		PRAC Recommendation - maintenance
II/0005/G	This was an application for a group of variations. Extension of indication to include treatment of patients below 2 months of age based on interim results from study BN40703 (RAINBOWFISH). The	20/07/2023	16/08/2023	SmPC, Labelling and PL	Please refer to Scientific Discussion 'EMEA/H/C/001899/II/0005/G

	pivotal study RAINBOWFISH is an ongoing phase II multicentre, open-label, and single-arm study designed to evaluate the efficacy, safety, tolerability, and PK/PD of risdiplam in pre-symptomatic infants below 2 months of age who were genetically diagnosed with SMA. As a consequence, SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated in accordance. In addition, the MAH took the opportunity to make some editorial improvements in the product information. A revised RMP version 1.1 was also submitted as part of the application. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one B.IV.1.b - Change of a measuring or administration device - Deletion of a device B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking				
II/0011	Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to delete an existing warning on "Use with SMA gene therapy" and to update the safety profile and efficacy data in patients previously treated with other SMA-modifying therapies based on the 24-month primary analysis data from study BP39054 (JEWELFISH); this is a multicenter, open-label study to investigate the safety, tolerability, and	20/04/2023	16/08/2023	SmPC	Section 4.4 has been updated to delete an existing warning on "Use with SMA gene therapy". Sections 4.8 and 5.1 have been updated to add information on the safety and efficacy profiles in patients previously treated with other SMA-modifying therapies based on JEWELFISH study. Section 5.2 has been updated with PK data from the same study.

	pharmacokinetics/pharmacodynamics of risdiplam in adult and paediatric patients with SMA. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10925 /202208	Periodic Safety Update EU Single assessment - risdiplam	16/03/2023	n/a		PRAC Recommendation - maintenance
IB/0014/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	22/02/2023	n/a		
IB/0015/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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	03/02/2023	n/a		

N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/02/2023	16/08/2023	PL	
IA/0013	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/12/2022	n/a		
IAIN/0009/G	This was an application for a group of variations. B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	13/10/2022	n/a		
PSUSA/10925 /202202	Periodic Safety Update EU Single assessment - risdiplam	01/09/2022	n/a		PRAC Recommendation - maintenance
IB/0006	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	17/06/2022	21/09/2022	SmPC and PL	
IA/0007	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	28/03/2022	n/a		
PSUSA/10925 /202108	Periodic Safety Update EU Single assessment - risdiplam	10/03/2022	n/a		PRAC Recommendation - maintenance

II/0003	Update of section 4.8 of the SmPC to add undesirable effects based on post-marketing experience. The Package Leaflet (PL) is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of local representatives in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/11/2021	21/09/2022	SmPC and PL	Section 4.8 of the SmPC has been updated to include Cutaneous Vasculitis as an undesirable effect with frequency not known based on post-marketing experience. For more information, please refer to the Summary of Product Characteristics.
II/0002	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/10/2021	21/09/2022	SmPC and PL	
IB/0001	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/05/2021	n/a		