Qarziba

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
II/0043	Update of sections 4.1, 4.2 and 5.1 of the SmPC based on final results from study APN311-202V3 listed as a Specific Obligation in the Annex II of the Product Information. This is a Phase I/II dose schedule finding study of Ch14.18/CHO continuous infusion combined with subcutaneous aldesleukin	12/10/2023		SmPC and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No' SmPC new text The safety of dinutuximab beta has been evaluated in 791 patients with high-risk and relapsed/refractory neuroblastoma, who received it as a continuous infusion

[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).

	(IL-2) in patients with primary refractory or relapsed neuroblastoma. In addition, the MAH took the opportunity to update Annex II section E. 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				(212) or as repeated daily infusions (416). It was combined with 13 cis retinoic in most patients and with IL 2 in 307 patients. The most common adverse reactions were pyrexia (86%) and pain (57%) that occurred despite analgesic treatment. Other frequent adverse reactions were hypersensitivity (74.1%), vomiting (55%), diarrhoea (52%), capillary leak syndrome (36%), Anaemia (49%), neutropenia (46%), thrombocytopenia (42%) and hypotension (41%).
IAIN/0054/G	This was an application for a group of variations. 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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.1 - Administrative change - Change in the name and/or address of the MAH	17/07/2023		SmPC, Annex II, Labelling and PL	
PSUSA/10597 /202211	Periodic Safety Update EU Single assessment - dinutuximab beta	08/06/2023	n/a		PRAC Recommendation - maintenance
IB/0052	B.I.b.2.e - Change in test procedure for AS or	13/04/2023	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0051/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation A.6 - Administrative change - Change in ATC Code/ATC Vet Code	31/03/2023		SmPC	
IB/0048/G	This was an application for a group of variations. 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.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.II.d.z - Change in control of the Finished Product - Other variation B.II.d.z - Change in control of the Finished Product - 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	08/02/2023	n/a		

	specification parameter to the specification with its corresponding test method B.II.d.z - Change in control of the Finished Product - Other variation				
II/0044	Update of sections 4.2, 4.4 and 4.8 of the SmPC with new safety information regarding central nervous system toxicity based on post-marketing safety report and literature. The package leaflet of the Product Information is amended accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2022	23/01/2023	SmPC and PL	SmPC new text Treatment with dinutuximab beta should be permanently discontinued if the following toxicities occur: • grade 3 or 4 anaphylaxis • prolonged grade 2 peripheral motor neuropathy • grade 3 peripheral neuropathy • grade 3 vision eye toxicity • grade 4 hyponatremia (< 120 mEq/L) despite appropriate fluid management • recurrent or grade 4 capillary leak syndrome (requires ventilator support) • severe central neurotoxicity that includes grade 3 or 4 with substantial prolonged neurological deficit without any detectable reason, recurrent grade 1-3 neurotoxicity, and permanent neurological deficit • all grades of posterior reversible encephalopathy syndrome and transverse myelitis Central neurotoxicity has been reported following treatment with Qarziba. If central neurotoxicity occurs the infusion should be interrupted immediately and the patient treated symptomatically, other influencing factors such as active infection, metastatic spread of neuroblastoma to CNS, neurotoxic concomitant medications should be ruled out. Treatment with dinutuximab beta should be permanently discontinued following the occurrence of severe

					neurotoxicity that includes grade 3 or 4 central neurotoxicity with substantial prolonged neurological deficit without any detectable reason, recurrent grade 1-3 neurotoxicity and/or permanent neurological deficit and all grades of posterior reversible encephalopathy syndrome and transverse myelitis. Reports of central neurotoxicity and severe neurotoxicity have been received including posterior reversible encephalopathy syndrome (0.7%) and seizures (1.7%).
IB/0049	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	05/01/2023	n/a		
S/0046	Annual re-assessment.	13/10/2022	09/12/2022	Annex II	
II/0047	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	06/10/2022	n/a		
II/0045	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	01/09/2022	09/12/2022	SmPC	
PSUSA/10597 /202111	Periodic Safety Update EU Single assessment - dinutuximab beta	10/06/2022	n/a		PRAC Recommendation - maintenance
IB/0042	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	24/05/2022	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0041	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	26/04/2022	n/a		
IB/0040	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	15/03/2022	n/a		
IB/0037	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	08/02/2022	n/a		
II/0035/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	27/01/2022	n/a		

	control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method				
IB/0031	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	13/01/2022	n/a		
R/0029	Renewal of the marketing authorisation.	11/11/2021	06/01/2022		
IB/0036	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	04/01/2022	n/a		
IB/0033	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/12/2021	n/a		
IB/0032	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/12/2021	n/a		
S/0028	Annual re-assessment.	14/10/2021	n/a		
II/0027/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC	16/09/2021	06/01/2022	SmPC, Labelling and PL	

	Code/ATC Vet Code 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				
IB/0026	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	03/08/2021	n/a		
PSUSA/10597 /202011	Periodic Safety Update EU Single assessment - dinutuximab beta	10/06/2021	n/a		PRAC Recommendation - maintenance
IAIN/0025	A.1 - Administrative change - Change in the name and/or address of the MAH	29/03/2021	06/01/2022	SmPC, Labelling and PL	
S/0022	Annual re-assessment.	15/10/2020	n/a		
IAIN/0023	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	28/09/2020	n/a		

PSUSA/10597 /201911	Periodic Safety Update EU Single assessment - dinutuximab beta	11/06/2020	n/a		PRAC Recommendation - maintenance
II/0015	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	12/03/2020	n/a		
IB/0021	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	03/03/2020	n/a		
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	19/12/2019	09/06/2020	SmPC and Annex II	
PSUSA/10597 /201905	Periodic Safety Update EU Single assessment - dinutuximab beta	28/11/2019	n/a		PRAC Recommendation - maintenance
IA/0018/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.4 - Administrative change - Change in the name	21/11/2019	09/06/2020	Annex II	

	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				
S/0016	Annual re-assessment.	17/10/2019	n/a		
PSUSA/10597 /201811	Periodic Safety Update EU Single assessment - dinutuximab beta	14/06/2019	n/a		PRAC Recommendation - maintenance
IAIN/0014/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.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	07/06/2019	09/06/2020	Annex II and PL	
IB/0013/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	17/04/2019	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/03/2019	09/06/2020	Labelling	
T/0010	Transfer of Marketing Authorisation	28/01/2019	11/03/2019	SmPC, Labelling and PL	
IB/0009/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	17/01/2019	n/a		
PSUSA/10597 /201805	Periodic Safety Update EU Single assessment - dinutuximab beta	29/11/2018	n/a		PRAC Recommendation - maintenance
S/0006	First annual re-assessment	26/07/2018	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 Qarziba should be maintained.
IB/0007	B.I.d.1.a.4 - Stability of AS - Change in the re-test	19/07/2018	n/a		

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
PSUSA/10597 /201711	Periodic Safety Update EU Single assessment - dinutuximab beta	17/05/2018	n/a		PRAC Recommendation - maintenance
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)	05/03/2018	19/07/2018	SmPC	
IAIN/0003	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	27/11/2017	19/07/2018	SmPC, Labelling and PL	
IAIN/0002	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	04/08/2017	19/07/2018	SmPC, Labelling and PL	
T/0001	Transfer of Marketing Authorisation	15/06/2017	17/07/2017	SmPC, Labelling and PL	