Yescarta

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
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2023		Labelling	
PSUSA/10703 /202204	Periodic Safety Update EU Single assessment - axicabtagene ciloleucel	01/12/2022	n/a		PRAC Recommendation - maintenance

[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).

II/0046	Extension of indication to include treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) for Yescarta; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the product information with minor editorial changes. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/09/2022	14/10/2022	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Yescarta-II-46'
IB/0055	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/10/2022	n/a		
WS/2247	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	15/09/2022	n/a		
PSUSA/10703	Periodic Safety Update EU Single assessment -	23/06/2022	17/08/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending

/202110	axicabtagene ciloleucel				the variation to terms of the Marketing Authorisation(s)' for PSUSA/10703/202110.
IB/0054	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	09/08/2022	n/a		
IB/0053	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/08/2022	n/a		
WS/2269	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	23/06/2022	n/a		
II/0042	Extension of indication to include the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy. Consequently, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC and Package Leaflet are proposed to be updated. As a consequence, the RMP (version 7.0) has been updated to align with the indication extension. In addition, the applicant has taken the opportunity to make minor editorial corrections throughout the SmPC and package leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/04/2022	21/06/2022	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Yescarta-H-C-004480/II/0042"

WS/2194	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	22/04/2022	n/a		
WS/2197	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	24/02/2022	n/a		
II/0040	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/02/2022	n/a		
WS/2181	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	27/01/2022	n/a		

PSUSA/10703 /202104	Periodic Safety Update EU Single assessment - axicabtagene ciloleucel	02/12/2021	n/a		PRAC Recommendation - maintenance
IB/0043/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	16/11/2021	n/a		
WS/2071	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	16/09/2021	n/a		
PSUSA/10703 /202010	Periodic Safety Update EU Single assessment - axicabtagene ciloleucel	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0038	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	30/04/2021	n/a		
IB/0036	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	23/04/2021	n/a		

	variation				
II/0035	B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	22/04/2021	n/a		
II/0028	Update of section 4.8 of the SmPC on cytokine release syndrome (CRS) and neurologic adverse reaction grading and management and update of section 5.1 of the SmPC to include data from 36-month and 48-month analyses from ZUMA-1 study Cohorts 1 and 2. The Package leaflet is updated accordingly. In addition, other minor updates are included in the product information. The RMP (version 3.5) has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2021		SmPC, Labelling and PL	For more information, please refer to the Summary of Product Characteristics.
IB/0037	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	31/03/2021	n/a		
II/0031	B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a	25/03/2021	n/a		

	method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol				
II/0030	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	25/03/2021	n/a		
II/0033	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	28/01/2021	n/a		
IA/0032	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	02/12/2020	n/a		
PSUSA/10703 /202004	Periodic Safety Update EU Single assessment - axicabtagene ciloleucel	26/11/2020	n/a		PRAC Recommendation - maintenance
IB/0029	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	29/10/2020	n/a		
IA/0027	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	07/08/2020	n/a		
IA/0025	B.I.a.2.a - Changes in the manufacturing process of	15/07/2020	n/a		

	the AS - Minor change in the manufacturing process of the AS				
IA/0024	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	07/07/2020	n/a		
II/0015	Changes to the manufacturing process of the biological active substance, axicabtagene ciloleucel, to extend the storage time for which the apheresis starting material used to isolate the PBMC Intermediate can be held. The apheresis material shipping temperature range can be extended from, between 2 and 10°C for a maximum time of 48 hours, to between 2°C and 16°C with a maximum shipping duration 72 hours. The requested variation proposed no amendments to the Product Information. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	25/06/2020	n/a		
IAIN/0023	A.1 - Administrative change - Change in the name and/or address of the MAH	22/06/2020	25/11/2020	SmPC, Labelling and PL	
IB/0020	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	11/06/2020	25/11/2020	Annex II	

II/0021	Update of the SmPC, Annex II, package leaflet and RMP to change the dose of tocilizumab to one dose instead of four doses in order to manage the Cytokine Release Syndrome. In addition, treatment centres should have access to an additional dose within 8 hours of each previous dose. Additional changes to the SmPC have been made with regards to the wording on GMO requirements. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/05/2020	25/11/2020	SmPC, Labelling and PL	Update of the SmPC, Annex II, package leaflet and RMP to change the dose of tocilizumab to one dose instead of four doses in order to manage the Cytokine Release Syndrome. In addition, treatment centres should have access to an additional dose within 8 hours of each previous dose. Additional changes to the SmPC have been made with regards to the wording on GMO requirements.
PSUSA/10703 /201910	Periodic Safety Update EU Single assessment - axicabtagene ciloleucel	14/05/2020	n/a		PRAC Recommendation - maintenance
IA/0022	A.7 - Administrative change - Deletion of manufacturing sites	11/05/2020	25/11/2020	Annex II and PL	
II/0019	B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	26/03/2020	n/a		
II/0018	B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	26/03/2020	n/a		
IB/0016	B.I.a.1.z - Change in the manufacturer of AS or of a	29/01/2020	n/a		

	starting material/reagent/intermediate for AS - Other variation				
PSUSA/10703 /201904	Periodic Safety Update EU Single assessment - axicabtagene ciloleucel	14/11/2019	13/01/2020	SmPC and Labelling	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10703/201904.
IB/0013	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	10/12/2019	25/11/2020	SmPC, Annex II, Labelling and PL	
II/0011	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	17/10/2019	n/a		
II/0012	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	19/09/2019	n/a		
II/0008	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	19/09/2019	n/a		
II/0007	B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the	25/07/2019	n/a		

	change requires an assessment of comparability				
II/0006	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	27/06/2019	n/a		
IB/0009	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/06/2019	n/a		
PSUSA/10703 /201810	Periodic Safety Update EU Single assessment - axicabtagene ciloleucel	16/05/2019	n/a		PRAC Recommendation - maintenance
II/0003	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2019	21/10/2019	SmPC, Annex II, Labelling and PL	In the 24-month follow-up analysis of study ZUMA-1 and based on the mITT population (results from an independent review committee), the Objective Response Rate and the Complete Response rate were 74% and 54%, respectively. The median time to response was 1.0 months (range: 0.8 to 12.2 months). The Duration of Response was longer in patients who achieved Complete Response compared to patients with a best response of Partial Response. Of the 55 patients who achieved CR, 7 patients had SD and 10 had PR at their initial tumour assessment and converted to CR as late as 12 months after YESCARTA infusion. Median duration of response and median overall survival have not been reached. Due to the on-target, off-tumour effect of YESCARTA, a period of B-cell aplasia is expected following treatment. Among 73 patients with evaluable samples at baseline, 40% had detectable B cells; the B cell aplasia observed in the majority of patients at baseline was attributed to prior therapies. Following YESCARTA treatment, the proportion of

					patients with detectable B cells decreased: 20% had detectable B cells at Month 3, and 22% had detectable B cells at Month 6. The initiation of B cell recovery was first noted at Month 9, when 56% of patients had detectable B- cells. This trend of B- cell recovery continued over time, as 64% of patients had detectable B- cells at Month 18, and 77% of patients had detectable B- cells at Month 24. It is important to note that patients were not required to be followed after they progressed; thus, the majority of patients with evaluable samples were responders. For more information please refer to the Summary of Product Characteristics.
IB/0002	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/01/2019	21/10/2019	Annex II	
IB/0004	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	09/01/2019	n/a		
IAIN/0001	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	19/10/2018	21/10/2019	Annex II and PL	