CARVYKTI

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/0034	Submission of an updated RMP version 6.1 in order to add a new important identified risk of "Secondary malignancy of T-cell origin", to change the important potential risk of "Second primary malignancies" to "Second primary malignancy except secondary malignancy of T-cell origin", and to include an	25/04/2025	n/a		Not applicable

[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).

	additional pharmacovigilance activity for testing of secondary malignancies of T-cell origin, following the PRAC recommendation for the Secondary malignancy of T-cell origin signal (EPITT no: 20040). The final version of the RMP (v6.1) includes consolidation of recent approved parallel RMP version 5.6 in procedure EMEA/H/C/005095/II/0036 and further updates the important potential risk of "Second primary malignancy except secondary malignancy of T-cell origin" to "Secondary malignancy except those of T cell and myeloid origin" as matter of combination of the two RMP versions. 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				
II/0036	Update of sections 4.8, and 5.1 of the SmPC in order to update the list of adverse drug reactions (ADRs), and update clinical efficacy and safety information based on second interim analysis from study 68284528MMY3002 (CARTITUDE-4); this is a phase 3 randomized study comparing ciltacabtagene autoleucel, a chimeric antigen receptor T cell (CAR-T) therapy directed against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in subjects with relapsed and lenalidomide-refractory multiple myeloma;	27/03/2025		SmPC and PL	Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), including cases with fatal outcomes, have occurred in patients after CARVYKTI infusion. As well, the PI has been updated to include "Secondary malignancy of myeloid origin" with a common frequency and provide updates of the efficacy data of longer follow up of the comparative study for the approval of carvykti. For more information, please refer to the Summary of Product Characteristics.

	furthermore, the procedure updates section 4.4 and 4.8 of the SmPC to implement safety information regarding secondary malignancy of myeloid origin included with common frequency as also discussed during the parallel PSUR (EMEA/H/C/PSUSA/00011000/202408). The package leaflet has been updated accordingly. Annex II is also updated to reflect the changes in the educational material regarding risk of secondary malignancies of myeloid origin. The RMP version 5.6 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives for Germany, Greece, Slovenia and United Kingdom(Northern Ireland) in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/11000 /202408	Periodic Safety Update EU Single assessment - ciltacabtagene autoleucel	13/03/2025	n/a		PRAC Recommendation - maintenance
II/0037	B.II.c.3.b - Change in source of an excipient or reagent with TSE risk - Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability	27/02/2025	n/a		
IB/0039	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	10/02/2025	n/a		

IB/0040	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	04/02/2025	n/a		
II/0035	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	30/01/2025	n/a		
IB/0038	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	28/01/2025	n/a		
IB/0031	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	11/10/2024	n/a		
PSUSA/11000 /202402	Periodic Safety Update EU Single assessment - ciltacabtagene autoleucel	03/10/2024	n/a		PRAC Recommendation - maintenance
IB/0029/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.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	19/09/2024	n/a		
II/0027/G	This was an application for a group of variations.	19/09/2024		Annex II and	The Annex II and IIIB have been updated with the following site:

	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 control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method 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.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.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method 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			PL	The new manufacturing and batch release site for active substance/finished product: Janssen Pharmaceutica Technologiepark-Zwijnaarde 73 9052, Ghent Belgium
IB/0032	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	22/08/2024	n/a		

IAIN/0030	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/07/2024		SmPC, Annex II and PL	
II/0023	B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	25/04/2024	n/a		
II/0021	Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an IMiD and a PI, have demonstrated disease progression on the last therapy and are refractory to lenalidomide for CARVYKTI, based on interim results from study MMY3002 listed as a specific obligation (SOB/006) in the Annex II. This is an ongoing, Phase 3, randomized, open-label, multicentre study to determine whether treatment with cilta-cel provides an efficacy benefit compared to standard therapy in participants with relapsed and lenalidomide-refractory multiple myeloma. As a consequence, sections 4.1, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The SOB is considered fulfilled and therefore deleted from Annex II. Version 4.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II of the PI. As part of the application the MAH is requesting a 1-year extension of the market protection. C.I.6.a - Change(s) to therapeutic indication(s) -	22/02/2024	19/04/2024	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Carvykti-H-C-5095-II-0021'.

	Addition of a new therapeutic indication or modification of an approved one				
PSUSA/11000 /202308	Periodic Safety Update EU Single assessment - ciltacabtagene autoleucel	11/04/2024	n/a		PRAC Recommendation - maintenance
R/0025	Renewal of the marketing authorisation.	25/01/2024	11/03/2024		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for CARVYKTI, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion and without prejudice to any of the ongoing scientific assessments.
PSUSA/11000 /202302	Periodic Safety Update EU Single assessment - ciltacabtagene autoleucel	12/10/2023	07/12/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/11000/202302.
II/0018	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 control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	09/11/2023	n/a		
IB/0024	B.II.g.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	27/10/2023	n/a		

IA/0022	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	25/07/2023	07/12/2023	SmPC	
II/0019	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 control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	20/07/2023	n/a		
II/0016	B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	22/06/2023	n/a		
IB/0020	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	19/06/2023	n/a		
IB/0015/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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	28/04/2023	n/a		

II/0005	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	30/03/2023	n/a		
IB/0014	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	28/03/2023	n/a		
R/0008	Renewal of the marketing authorisation.	26/01/2023	24/03/2023	SmPC, Annex II and PL	The CAT/CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for CARVYKTI, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IB/0010/G	This was an application for a group of variations. B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product 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	17/03/2023	n/a		

	batch control/testing takes place				
PSUSA/11000 /202208	Periodic Safety Update EU Single assessment - ciltacabtagene autoleucel	16/03/2023	n/a		PRAC Recommendation - maintenance
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/03/2023	07/12/2023	PL	
IB/0012	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	17/02/2023	n/a		
IB/0011	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	14/02/2023	n/a		
II/0004/G	This was an application for a group of variations. Grouped application comprising two type II variations as follows: - Update of section 4.4 of the SmPC in order to add a new warning on increased risk of severe/fatal COVID-19 infections following Covid-19 signal evaluation from the ongoing study 68284528MMY3002 (CARTITUDE-4) based on a cumulative review of all clinical trials, registries and literature. - Update of section 4.4 of the SmPC in order to add a new warning Risk of severe bleeding in the context of hemophagocytic lymphohistiocytosis syndrome	15/12/2022	24/03/2023	SmPC and PL	SmPC new text: Patients who develop HLH may have an increased risk of severe bleeding. Patients treated with CARVYKTI may be at an increased risk of severe/fatal COVID-19 infections. Patients should be counselled on the importance of prevention measures. For more information, please refer to the Summary of Product Characteristics.

	(HLH) following a signal evaluation from the ongoing study 68284528MMY3002 (CARTITUDE-4) based on cumulative review of all clinical trials, registries and literature. The Package Leaflet is updated accordingly. The RMP version 2.2 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0003	Update of sections 4.4 and 4.8 of the SmPC in order to update the existing warnings on cytokine release syndrome (CRS), neurologic toxicities and grading of related events and to update the list of adverse drug reactions (ADRs) based on previously reviewed data from studies MMY2001 and MMY2003, and an additional internal characterisation of neurotoxicity risk; the Package Leaflet is updated accordingly. The RMP version 2.1 has also been submitted. 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	15/12/2022	24/03/2023	SmPC, Labelling and PL	For more information, please refer to the Summary of Product Characteristics.
IB/0007	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	24/11/2022	n/a		

	of the AS				
IB/0006	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	10/11/2022	n/a		
II/0002	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	10/11/2022	n/a		
IB/0001	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/10/2022	n/a		