Kymriah

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/0092	Update of section 4.2 of the SmPC in order to update the 'monitoring after infusion' recommendations, based on existing clinical trial data as well as literature references reporting real word experience. The Package Leaflet is updated accordingly. The RMP version 8.1 has also been submitted. In addition, the	27/03/2025		SmPC, Annex II and PL	SmPC new text The recommendations for monitoring patients after infusion have been revised as follows: - In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion

[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).

	MAH took the opportunity to introduce a minor change to the HCP educational programme in the Annex II in order to enhance readability. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				- After the first week following the infusion, the patient should be monitored at the physician's discretion. For more information, please refer to the Summary of Product Characteristics.
II/0086/G	This was an application for a group of variations. A grouped application consisting of: C.I.4: Update of section 4.4 of the SmPC in order to amend existing warnings on cytokine release syndrome based on literature. C.I.4: Update of section 4.4 of the SmPC in order to amend existing warnings on neurological adverse reaction based on literature. The Package Leaflet is updated accordingly. C.I.4: Update of section 4.4 of the SmPC in order to amend existing warnings on hypersensitivity reactions based on post marketing data and literature. The Package Leaflet is updated accordingly. In addition, a new warning of CD19-negative disease ALL patients has been included in section 4.4 of the SmPC. The MAH took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to	27/02/2025		SmPC, Annex II and PL	The table in section 4.4 of the SmPC on cytokine release syndrome management algorithm has been substituted by the following recommendation: To reduce the risk of or manage CRS complications (see above), patients treated with Kymriah may receive anti-interleukin-6-based intervention (e.g. tocilizumab) with or without a corticosteroid-based therapy. CRS management strategies may be implemented based on the most recent relevant treatment guidelines, including appropriate local institutional/academic guidelines. The following text has been added to section 4.4 with regards to ICANs: To reduce the risk of or manage neurological toxicities (including ICANS), patients treated with Kymriah may receive supportive treatment based on the most recent relevant guidelines, including appropriate local institutional/academic guidelines. And finally, the following new warning has been added to section 4.4 of the SmPC, at the request of CAT: CD19-negative B-cell ALL disease Kymriah is not recommended if the B-cell ALL patient has CD19-negative disease or an unconfirmed CD19 status.

	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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				For more information, please refer to the Summary of Product Characteristics.
IB/0093	B.II.d.z - Change in control of the Finished Product - Other variation	30/01/2025	n/a		
IB/0090	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/01/2025	n/a		To update the RMP with the recommendation following signal assessment if secondary malignancy of T-cell origin.
IAIN/0091/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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	18/11/2024	28/02/2025	Annex II and PL	
IB/0088/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	05/11/2024	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IA/0087	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	08/10/2024	n/a		
IB/0083	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	20/09/2024	n/a		
IB/0085	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/09/2024	n/a		
IB/0082	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	20/08/2024	n/a		

IAIN/0084	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/08/2024	28/02/2025	SmPC and PL	
IB/0081/G	This was an application for a group of variations. 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 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	08/07/2024	n/a		
IB/0080/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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 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	28/05/2024	n/a		

	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				
PSUSA/10702 /202308	Periodic Safety Update EU Single assessment - tisagenlecleucel	07/03/2024	n/a		PRAC Recommendation - maintenance
II/0079/G	This was an application for a group of variations. 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 B.I.z - Quality change - Active substance - Other variation	22/02/2024	n/a		
II/0075	Update of sections 5.1 and 5.2 of the SmPC to update efficacy and pharmacokinetic information based on final results from study CI.CTL019C2201 PAES in the Annex II (ANX008); this is a Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The RMP version 6 has also been submitted. In addition, Annex II.D of the product information is updated to reflect that the obligation to conduct the mention study is fulfilled. C.I.4 - Change(s) in the SPC, Labelling or PL due to	22/02/2024	28/02/2025	SmPC and Annex II	As a result of this variation, sections 5.1 and 5.2 of the SmPC are being updated to include the final results from study C2201. For more information, please refer to the Summary of Product Characteristics.

	new quality, preclinical, clinical or pharmacovigilance data				
II/0071	Update of sections 5.1 and 5.2 of the SmPC to update efficacy and pharmacokinetic information based on final results from study CCTL019B2202 (a phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia). Submission of cellular kinetic report for the B-cell acute lymphoblastic leukaemia (ALL) indication based on data from pivotal study CCTL019B2202 and the supportive study CCTL019B2205J involving paediatric ALL patients (partially fulfil REC). In addition, the MAH took this opportunity to introduce editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2024	28/02/2025	SmPC	For more information, please refer to the Summary of Product Characteristics.
IB/0076/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	05/01/2024	n/a		

IB/0077	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/11/2023	n/a		
IB/0074/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.c.1.z - Change in immediate packaging of the AS - Other variation	12/09/2023	n/a		
II/0069	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	20/07/2023	n/a		
IA/0073/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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	18/07/2023	n/a		

	corresponding test method				
II/0070/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	22/06/2023	n/a		
R/0068	Renewal of the marketing authorisation.	23/02/2023	26/04/2023	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Kymriah in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10702 /202208	Periodic Safety Update EU Single assessment - tisagenlecleucel	16/03/2023	n/a		PRAC Recommendation - maintenance
II/0050	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	15/12/2022	n/a		
IB/0064/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) A.7 - Administrative change - Deletion of manufacturing sites	28/10/2022	26/04/2023	Annex II	
IB/0066	B.I.z - Quality change - Active substance - Other variation	21/10/2022	n/a		

II/0059	Update of section 5.1 of the SmPC based on a subgroup analysis from CCTL019B2401 (B2401) disease registry listed as a PAES (ANX006) in the Annex II; this is a non-interventional study to evaluate the efficacy and safety of Kymriah in ALL patients below the age of 3 years. In addition, the MAH took the opportunity to update Annex II.D of the SmPC to reflect the fulfilment of the PAES. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2022	26/04/2023	SmPC and Annex II	SmPC new text: Section 4.8 of the SmPC: Paediatric population The safety of tisagenlecleucel in r/r B-cell ALL paediatric patients from 3 years of age and older was assessed in 212 patients in the pivotal study B2202 and the supportive studies B2205J and B2001X in which the majority of patients (81%) were under 18 years old (65/79 in B2202, 54/64 in B2205 and 52/69 in B2001X). The frequency, type and severity of adverse reactions in paediatric patients are reflected in "Summary of the safety profile" and in Table 2 above. The safety of tisagenlecleucel in r/r B-cell ALL paediatric patients below 3 years of age was assessed in the observational study B2401 (n=43) where the overall safety experience was generally consistent with the known safety profile of tisagenlecleucel. Section 5.1 of the SmPC: Study B2401 An observational study (B2401) was conducted to collect long-term safety and efficacy data in patients infused with tisagenlecleucel from the Center for International Blood and Marrow Transplant Research (CIBMTR) and European Society for Blood and Marrow Transplantation (EBMT) registries. The study included 617 (CIBMTR: 570; EBMT: 47) paediatric and young adult patients with r/r B-cell ALL at time of the data cut off. Kymriah manufacture for patients below 3 years of age and with low weight was feasible; 43 patients (CIBMTR: 40, EBMT: 3) were below 3 years of age at time of infusion. The median time from Kymriah infusion to the data cut off date of the paediatric

					and young adult patients with r/r B-cell ALL was 11.8 months for CIBMTR and 9.0 months for EBMT. Among the patients below 3 years of age included in the efficacy set (n=33), CR (including CRi) as BOR was reported for 26 patients (78.8%) (95% CI: 61.1, 91.0) and all 15 patients in CR (including CRi) and with reported MRD data were MRD negative during follow-up. The estimated DOR rate at month 12 was 62.7% (95% CI: 35.0, 81.3). The overall safety experience in patients below 3 years of age with r/r B-cell ALL was generally consistent with the known safety profile of tisagenlecleucel. For more information, please refer to the Summary of Product Characteristics.
II/0053	Submission of the results from study CCTL019H2301 (BELINDA) listed as an obligation in the Annex II of the Product Information. This is a randomised open-label parallel-group multicenter Phase III trial to evaluate the efficacy and safety of tisagenlecleucel in adult patients with relapsed or refractory B-cell aggressive NHL after failure of rituximab and anthracycline containing first-line immune-chemotherapy. The Annex II is updated accordingly. 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	13/10/2022	26/04/2023	Annex II	Not applicable For more information, please refer to the Summary of Product Characteristics.
IB/0065	B.I.a.2.a - Changes in the manufacturing process of	11/10/2022	n/a		

	the AS - Minor change in the manufacturing process of the AS				
II/0062	Submission of the final report from study CCTL019B2401 listed as a category 1 study in the Annex II of the Product Information in order to fulfil ANX/007.3. This is a sub-analysis (PAES) to assess efficacy in patients with relapsed or refractory diffuse large B-cell lymphoma based on data from the registry study to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel. The Annex II is updated accordingly. 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	15/09/2022	26/04/2023	Annex II	Not applicable For more information, please refer to the Summary of Product Characteristics.
II/0061/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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	15/09/2022	n/a		

II/0060	Update of section 4.2 of the SmPC in order to update the paediatric statement for the B-cell ALL indication and section 4.4 to update the warning on 'prior treatment with anti-CD19 therapy' as well as sections 4.4 and 4.8 in order to update safety data to reflect the pool of the 3 studies B2202, B2205J and B2001X. The proposed changes are in line with the request of the CHMP following the assessment of P46/012. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to correct the Complete Response Rate (CRR) 95% Confidence Interval (CI) on Enrolled set for E2202 study presented in Table 8 in section 5.1 of the SmPC. The RMP version 5.1 has also been submitted. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	15/09/2022	26/04/2023	SmPC and PL	SmPC new text: The existing warning in section 4.4 of the SmPC related to patients that had received prior anti-CD 19 therapy has been updated to include that 'while activity of tisagenlecleucel has been observed (in patients previously exposed to CD 19 directed therapy), data are currently too limited to make an adequate assessment of the benefit-risk profile in these patients.' Section 4.8 of the SmPC has been updated to reflect the updated safety data from studies B2202, B2205J and B2001X. For more information, please refer to the Summary of Product Characteristics.
II/0056	Update of sections 4.2 and 5.1 of the SmPC in order to update efficacy and safety information in paediatric population based on study CCTL019C2202, a phase II, single arm, multicenter open label trial to determine the safety and efficacy of tisagenlecleucel in pediatric patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL) (BIANCA). The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	15/09/2022	26/04/2023	SmPC and PL	Please refer to Scientific Discussion 'Kymriah-H-C-004090-II-0056' For more information, please refer to the Summary of Product Characteristics.

	new quality, preclinical, clinical or pharmacovigilance data				
II/0055	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	15/09/2022	n/a		
II/0058	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	21/07/2022	n/a		
IB/0057/G	This was an application for a group of variations. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.z - Change in control of the AS - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	02/06/2022	n/a		
II/0044	Extension of indication to include treatment of adult patients with relapsed or refractory follicular	24/03/2022	29/04/2022	SmPC, Annex	Please refer to Scientific Discussion 'Kymriah-H-C-4090-II-

	lymphoma (FL) after two or more lines of systemic treatment for Kymriah. As a consequence, Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and corresponding sections in the Package Leaflet are updated accordingly. The RMP has been updated to version 4.2 to align with the indication extension. The updates to Module 3 include mainly the incoming FL material characterization, final product characterization and FL batch analyses data. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			II and PL	0044’
II/0052	B.I.z - Quality change - Active substance - Other variation	22/04/2022	n/a		
IAIN/0054	B.II.g.3 - Deletion of an approved change management protocol related to the finished product	07/04/2022	n/a		
PSUSA/10702 /202108	Periodic Safety Update EU Single assessment - tisagenlecleucel	10/03/2022	n/a		PRAC Recommendation - maintenance
II/0049/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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	24/02/2022	n/a		

	biol. reference preparation not covered by an approved protocol				
IB/0048/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	07/02/2022	29/04/2022	SmPC	
IB/0051/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 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	03/02/2022	n/a		
II/0047	Update of sections 4.2 and 4.4 of the SmPC, Annex IID and PIL (information intended for healthcare professionals) in order to add statements for the use of Kymriah exceptionally during shortage of tocilizumab following the "CAT recommendation for the use of CAR-T cell-based therapies in EU during shortages of tocilizumab". C.I.4 - Change(s) in the SPC, Labelling or PL due to	16/12/2021	24/01/2022	SmPC, Annex II and PL	The product information has been amended to reflect that in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab should be available on-site prior to infusion. For more information, please refer to the Summary of Product Characteristics.

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0046/G	This was an application for a group of variations. B.z - Quality Change - Other variation B.z - Quality Change - Other variation B.z - Quality Change - Other variation	08/12/2021	n/a		
II/0040	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	14/10/2021	n/a		
IB/0042/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.II.e.z - Change in container closure system of the Finished Product - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.II.d.z - Change in control of the Finished Product - Other variation	12/10/2021	n/a		

PSUSA/10702 /202102	Periodic Safety Update EU Single assessment - tisagenlecleucel	30/09/2021	n/a		PRAC Recommendation - maintenance
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/09/2021	24/01/2022	PL	
IB/0043	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	10/09/2021	n/a		
IB/0039	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/06/2021	24/01/2022	SmPC and Annex II	
IB/0035/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.I.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile) 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 B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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	16/06/2021	n/a		

	material/intermediate 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				
IB/0036	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	04/06/2021	n/a		
IB/0037	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/05/2021	n/a		
IB/0033/G	This was an application for a group of variations. B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/04/2021	n/a		
IB/0034/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished	23/03/2021	24/01/2022	SmPC	

	product formulation - Change that does not affect the product information B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
PSUSA/10702 /202008	Periodic Safety Update EU Single assessment - tisagenlecleucel	11/03/2021	n/a		PRAC Recommendation - maintenance
X/0010	Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure	12/12/2019	04/03/2021		
II/0030	Update of section 5.1 of the SmPC to include the complete data set (updated overall survival analysis) of study CCTL019B2205J, a Phase II, single arm, multicenter study to determine the efficacy and safety of Kymriah in paediatric subjects with relapsed or refractory B-cell ALL. The clinical results have already been assessed in procedure EMA/H/C/004090/P46/011. In addition, the final ATC code for tisagenlecleucel (L01XX71) has been added as an editorial change. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	25/02/2021	24/01/2022	SmPC	SmPC new text: The supportive study B2205J (ENSIGN) was a multicentre single-arm phase II study in paediatric and young adult patients with r/r B-cell ALL. The study had similar study design and enrolled comparable patient populations as the pivotal study B2202. The main difference between the two studies was the definition of the primary efficacy endpoint ORR, which was measured within 6 months after Kymriah infusion in study B2205J compared to 3 months in the pivotal study. Of 75 patients enrolled, 64 received infusion of Kymriah; for 5 patients (6.7%), Kymriah could not be manufactured and 6 patients (8.0%) died while awaiting Kymriah manufacturing in the clinical study. The median duration of study follow-up defined as the time from Kymriah infusion to the date of completion or discontinuation from follow-up prior to the data cut-off date in the final analyses was 12.2 months (range: 0.4-49.3). The median time from Kymriah infusion to the data cut-off date was 31.7 months (range: 17.6-56.0). Among the patients infused, the median age was 12.5 years (range: 3 to 25), 34 (53.1%) were female and 30

					(46.9%) were male, 10.9% had primary refractory disease, 89.1% had relapsed disease, and 43.8% of patients had at least one prior haematopoietic stem cell transplant. Baseline disease characteristics were similar in the enrolled patients with regard to age (median age 13.0 years, range: 3 to 25), gender (46.7% female and 53.3% male), primary refractoriness (10.7%), and prior transplant history (42.7%). The majority of infused patients (57/64, 89.1%) received bridging chemotherapy while waiting for Kymriah. A total of 60 out of 64 patients (93.8%) who received Kymriah infusion also received lymphodepleting chemotherapy after enrolment and prior to infusion of a single dose of Kymriah. Efficacy was established through the primary endpoint of ORR, which included best overall response as CR or CRi that were maintained for at least 28 days within 6 months post infusion, as determined by IRC assessment, as well as secondary endpoints including DOR, proportion of patients who achieved CR or CRi with MRD negative disease status, and OS. Among the patients infused, ORR was demonstrated in 45 patients (70.3%; 59.4% CR and 10.9% CRi). CR/CRi with MRD negative bone marrow was reported in 43 patients (67.2%). The median DOR was not reached and the event free probability at 12 months was 70.5%. The survival probability at 24 months was 54.7%, and the median OS was estimated as 29.9 months (95% CI: 15.1, 42.4). The OS results were confirmed in an updated OS analyses (i.e. median OS 29.9 months [95% CI: 15.2, NE] with 57.6% survival probability at 24 months; with a median follow up for OS of 25.9 months), which included patients transitioned to a separate long term follow up study. Seven patients (10.9%) who achieved CR/CRi after

					Kymriah infusion proceeded to haematopoietic stem cell transplant while in remission during the study, of which 5 of the patients (7.8%) proceeded to transplant within the first 6 months post infusion. Efficacy results reported for the enrolled patients (n=75) demonstrate an ORR of 60.0% (50.7% CR and 9.3% CRi; 57.3% with MRD negative bone marrow). The reported overall survival in the enrolled population is in accordance with the infused population. For more information, please refer to the Summary of Product Characteristics.
IB/0032	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/12/2020	n/a		
IB/0031/G	This was an application for a group of variations. 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	18/12/2020	n/a		
II/0027	B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	10/12/2020	n/a		
II/0028/G	This was an application for a group of variations.	12/11/2020	n/a		

	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 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				
II/0026/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation 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 change requires an assessment of comparability	12/11/2020	n/a		
PSUSA/10702 /202002	Periodic Safety Update EU Single assessment - tisagenlecleucel	03/09/2020	n/a		PRAC Recommendation - maintenance
II/0025	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	23/07/2020	n/a		

IB/0024/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.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.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	17/07/2020	04/03/2021	Annex II and PL	
II/0022/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	25/06/2020	n/a		
II/0021/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a	28/05/2020	n/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 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				
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	21/04/2020	n/a		
IAIN/0020	B.II.g.3 - Deletion of an approved change management protocol related to the finished product	17/04/2020	n/a		
II/0017/G	This was an application for a group of variations. B.II.a.3.b.6 - Changes in the composition (excipients) of the finished product - Other excipients - Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level 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	26/03/2020	n/a		

IB/0018/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.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR	20/03/2020	n/a		
PSUSA/10702 /201908	Periodic Safety Update EU Single assessment - tisagenlecleucel	12/03/2020	n/a		PRAC Recommendation - maintenance

II/0013/G	This was an application for a group of variations. Submission of a group of 3 type II variations (C.I.4) to include: - Long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL based on the 24 months follow-up results from study CCTL019C2201 (update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC) - Interim results from study CCTL019B2202 (update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC) - Interim results from study CCTL019B2205J (update section 5.2 of the SmPC) The Marketing authorisation holder (MAH) took the opportunity to clarify the wording of the indication to include patients over 25 years of age and to introduce some minor editorial corrections throughout the SmPC and the Package Leaflet. The MAH also updated sections 4.2, 4.4, 4.8 of the SmPC, Annex II and the Package Leaflet with regards to the acceptability of having 1 dose of tocilizumab per patient per centre for the management of cytokine release syndrome. In addition, the MAH requested updates to sections 2.2 and 6.5 of the SmPC, the labelling and to the package leaflet to accommodate the administration of additional infusion bags, when applicable. The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Annex IIIA and Package Leaflet and to the Risk Management Plan (RMP). The	27/02/2020	04/03/2021	SmPC, Annex II and PL	This variation now clarifies that the indication also covers patients aged 25 years inclusive with B cell acute lymphoblastic leukaemia (ALL) and that two doses of tocilizumab should be available for use in the event of cytokine release syndrome and emergency equipment must be available per patient prior to infusion. The treatment centre must have access to additional doses of tocilizumab within 8 hours. Updated data are provided in section 5.1 of the SmPC for study B2202 and C2201 as well as updated data are also provided in section 5.2 of the SmPC. In addition, updates are being made to the sections 2.2 and 6.5 of the SmPC, the Package Leaflet and the Labelling to clarify accommodate the administration of additional infusion bags, when applicable.

	RMP version 2.1 has been agreed. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0014	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	30/01/2020	n/a		
IB/0015/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile)	05/11/2019	n/a		
II/0011	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	19/09/2019	n/a		
PSUSA/10702 /201902	Periodic Safety Update EU Single assessment - tisagenlecleucel	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0012	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	14/08/2019	n/a		

IB/0007	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	21/03/2019	n/a		
IA/0006/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.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	28/02/2019	n/a		
IB/0005/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a	13/02/2019	n/a		

	biological/immunological medicinal product				
IB/0002	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	08/02/2019	n/a		
IA/0004/G	This was an application for a group of variations. A.z - Administrative change - Other variation B.I.z - Quality change - Active substance - Other variation B.I.z - Quality change - Active substance - Other variation B.I.z - Quality change - Active substance - Other variation B.I.a.z - Change in manufacture of the AS - Other variation B.I.a.z - Change in manufacture of the AS - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/01/2019	n/a		
IB/0003	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	07/01/2019	n/a		

II/0001	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	13/12/2018	n/a		