BLINCYTO

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/0054	To update sections 4.2, 4.4, 4.8 of the SmPC to include Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS); and to update section D of Annex II to remove educational materials for physicians, pharmacists, and to include ICANS within neurologic events in educational	13/03/2025		SmPC, Annex II and PL	SmPC new text: ICANS, including Grade 3 and higher ICANS, were reported in clinical trials and with post-marketing experience. The most frequent clinical manifestations of ICANS were confusional state, aphasia, disorientation, altered state of consciousness, dysarthria, encephalopathy, seizure, mental

[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).

	material for nurses and patient/caregivers and patient alert card following the outcome of PSUR procedure EMEA/H/C/PSUSA/00010460/202212. The Package Leaflet is updated accordingly. The RMP version 17.2 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				status changes, somnolence and dysgraphia. Relevant dose management of Blyncito in case of ICANs have been implemented in the posology section of the SmPC. Relevant educational material high level requirement have also been included in the annex II and the RMP for risk minimisation management of ICANs. For more information, please refer to the Summary of Product Characteristics.
II/0056	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	12/12/2024	23/01/2025	SmPC and PL	Please refer to Scientific Discussion 'Blincyto-H-C-003731-II-0056'.
IB/0060/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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	11/12/2024	n/a		
IA/0059	A.7 - Administrative change - Deletion of manufacturing sites	28/06/2024	n/a		
IB/0057	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/04/2024	29/05/2024		

II/0053/G	This was an application for a group of variations. A grouped application consisting of: Type II (C.I.4): Update of sections 6.6 of the SmPC in order to add a statement that the administration of Blincyto for BSA of less than 0.4 m2 has not been established. In addition, the MAH took the opportunity to update the name of ATC pharmacological subgroup according to WHO ATC Index and to delete "intravenous catheter" from the important note statement regarding flushing and to introduce minor editorial changes to the PI. The Package Leaflet is updated accordingly. Type IB (C.I.11.z): Update of the due dates for post-authorisation safety studies 20150136 and 20180130 in the Annex II D in order to align with the RMP version 16.0, following commitment agreed on during procedure EMEA/H/C/003731/IB/0050. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/02/2024	29/05/2024	SmPC, Annex II, Labelling and PL	SmPC new text: *The safety of the administration of BLINCYTO for BSA of less than 0.4 m2 has not been established. For more information, please refer to the Summary of Product Characteristics.
IB/0055	C.I.3.z - 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 - Other variation	20/02/2024	29/05/2024	SmPC	

II/0051	Update of section 4.8 of the SmPC in order to update immunogenicity information to remove reference to antibody testing based on an analysis of all completed clinical studies and post-marketing data. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/10/2023	29/05/2024	SmPC	SmPC new text (section 4.8): In clinical studies of adult ALL patients treated with BLINCYTO, less than 2% tested positive for anti-blinatumomab antibodies. Of patients who developed anti-blinatumomab antibodies, the majority had in vitro neutralizing activity. No anti blinatumomab antibodies were detected in clinical studies of paediatric patients with relapsed or refractory ALL treated with blinatumomab. Anti-blinatumomab antibody formation may affect the pharmacokinetics of BLINCYTO. Overall, the totality of clinical evidence supports the finding that anti-blinatumomab antibodies are not suggestive of any clinical impact on the safety or effectiveness of BLINCYTO. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10460 /202212	Periodic Safety Update EU Single assessment - blinatumomab	06/07/2023	n/a		PRAC Recommendation - maintenance
IB/0052/G	This was an application for a group of variations. B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	19/06/2023	n/a		

	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				
IB/0050	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/04/2023	n/a		
R/0048	Renewal of the marketing authorisation.	26/01/2023	09/03/2023	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of BLINCYTO in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0047/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method 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	01/09/2022	09/03/2023	SmPC and Annex II	The SmpC section 5.1 has been modified (Change in ATC Code from L01XC19 to L01FX07) The section A in Annex II (Manufacturers of the biological active substance and manufacturers responsible for batch release) has been updated as follows: Addition of the manufacturer "Amgen Inc One Amgen Center Drive Thousand Oaks, CA 91320 USA"

PSUSA/10460 /202112	Periodic Safety Update EU Single assessment - blinatumomab	07/07/2022	n/a		PRAC Recommendation - maintenance
II/0045	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	23/06/2022	n/a		
IA/0044	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	04/10/2021	n/a		
IB/0043	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	02/09/2021	n/a		
PSUSA/10460 /202012	Periodic Safety Update EU Single assessment - blinatumomab	08/07/2021	n/a		PRAC Recommendation - maintenance
II/0039	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/06/2021	n/a		
II/0038	Extension of indication to include the use of blinatumomab as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. In	20/05/2021	24/06/2021	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Blincyto-H-C-3731-II-0038'.

	addition, section 6.6 of the SmPC is updated to improve readability of the instructions for preparation. The Package Leaflet is updated in accordance. Version 15 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0042	A.7 - Administrative change - Deletion of manufacturing sites	07/05/2021	n/a		
IB/0041	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/03/2021	24/06/2021	SmPC, Annex II and PL	
PSUSA/10460 /202006	Periodic Safety Update EU Single assessment - blinatumomab	28/01/2021	26/03/2021	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10460/202006.
II/0030	To modify the approved therapeutic indication to include the treatment of Philadelphia chromosome positive CD19 positive B-cell precursor acute lymphoblastic leukaemia (ALL) in adult patients with relapsed or refractory ALL who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the PL are updated accordingly. The updated RMP version 10.0 has also been submitted. The variation leads to amendments to the Summary	15/10/2020	22/12/2020	SmPC and PL	Please refer to Scientific Discussion Blincyto EMEA/H/C/003731/II/0030

	of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10460 /201912	Periodic Safety Update EU Single assessment - blinatumomab	09/07/2020	n/a		PRAC Recommendation - maintenance
II/0033	Submission of an updated RMP version 11 is in line with the guideline on Good Pharmacovigilance Practices (GVP) Module V on RMP. In accordance with the RMP update, the protocol for Category 1 PASS 20150136 has been updated and the enrolment period for the study has been extended by 1 year. The milestones in the RMP were updated accordingly. In addition, the RMP includes a proposed update to the milestone of the Category 3 PASS 20180138. The requested variation proposed amendments to the Risk Management Plan (RMP). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	11/06/2020	n/a		
II/0036	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	28/05/2020	n/a		

	of studies to the competent authority				
II/0034/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/04/2020	n/a		
PSUSA/10460 /201906	Periodic Safety Update EU Single assessment - blinatumomab	16/01/2020	n/a		PRAC Recommendation - maintenance
IB/0032	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/09/2019	21/10/2019	SmPC	
PSUSA/10460 /201812	Periodic Safety Update EU Single assessment - blinatumomab	14/06/2019	n/a		PRAC Recommendation - maintenance
II/0011	Extension of indication to include the treatment of adults with Philadelphia chromosome-negative CD19 positive B precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% for BLINCYTO monotherapy; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 9.1) are updated in accordance. In addition, the Marketing authorisation holder took the opportunity to update the contact details of the Portuguese and Irish local representatives in the Package Leaflet.	15/11/2018	18/01/2019	SmPC and PL	Please refer to the Scientific Discussion Blincyto-H-C-3731-II-11

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10460 /201806	Periodic Safety Update EU Single assessment - blinatumomab	17/01/2019	n/a		PRAC Recommendation - maintenance
IA/0028	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	30/08/2018	n/a		
II/0018	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/07/2018	23/08/2018	SmPC, Annex II and PL	
II/0009	Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC, Annex II and Package Leaflet based on the clinical study 103311 (TOWER): a Study of BITE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukaemia (ALL). The RMP (version 7.0) has been updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took this opportunity to make editorials changes in section 6.6 of the SmPC. Finally, the CHMP recommends the granting of a marketing authorisation no longer subject to specific obligations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	25/01/2018	18/06/2018	SmPC, Annex II and PL	In this variation the marketing authorisation holder submitted data from study 00103311 (TOWER): A Study of blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukaemia (ALL). The primary endpoint was overall survival (OS) defined as the time of randomization until death due to any cause. Key secondary endpoints included complete remission (CR), complete remission with partial hematologic recovery (CRh*), complete remission with incomplete hematologic recovery (CRi) and minimal residual disease (MRD). In this study statistically and clinically significant increases of primary endpoint OS and secondary endpoints CR/CRh*/CRi and MRD negativity were observed in the blinatumomab arm as compared to the SOC chemotherapy arm (7.7 months vs 4.0 months, 43.9% vs 24.3%, 23.6% vs 9.0% respectively). In

	data				conclusion, the controlled data of the Phase 3 study 00103311 confirmed the efficacy and safety of blinatumumab and the CHMP agreed on the fulfilment of the specific obligation. Please refer to the assessment report: Blincyto EMEA/H/C/003731/II/0009
PSUSA/10460 /201712	Periodic Safety Update EU Single assessment - blinatumomab	14/06/2018	n/a		PRAC Recommendation - maintenance
IG/0946	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	04/06/2018	23/08/2018	PL	
R/0013	Renewal of the marketing authorisation.	25/01/2018	19/04/2018		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations as assessed trough the parallel variation EMEA/H/C/003731/II/0009 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. Furthermore, the CHMP considered that, as all Specific Obligations have been fulfilled, there are no remaining grounds for the marketing authorisations to remain conditional and therefore recommends the granting of the MA no longer subject to Specific Obligations for BLINCYTO. The changes to the Product Information are further described as part of variation EMEA/H/C/003731/II/009.
PSUSA/10460 /201706	Periodic Safety Update EU Single assessment - blinatumomab	25/01/2018	23/03/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10460/201706.
II/0020/G	This was an application for a group of variations. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products 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	14/12/2017	n/a		
IG/0853	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	10/11/2017	23/03/2018	Annex II and PL	
PSUSA/10460 /201612	Periodic Safety Update EU Single assessment - blinatumomab	20/07/2017	18/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10460/201612.
IB/0015/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	31/07/2017	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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 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				
IB/0016	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	28/07/2017	23/03/2018	SmPC and PL	
IA/0017/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) A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	07/07/2017	n/a		

IB/0012	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/04/2017	n/a		
IB/0007	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/12/2016	n/a		
PSUSA/10460 /201605	Periodic Safety Update EU Single assessment - blinatumomab	01/12/2016	n/a		PRAC Recommendation - maintenance
IB/0008	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	04/11/2016	n/a		
II/0003	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning with regards to pancreatitis, and to section 4.4 to emphasise the mitigation of the risk of Cytokine Release Syndrome. In addition the MAH took the opportunity to make administrative changes section 4.2 and 5.1. 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	15/09/2016	21/10/2016	SmPC and PL	
R/0004	Renewal of the marketing authorisation.	21/07/2016	22/09/2016		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 BLINCYTO, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IB/0005	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	05/08/2016	21/10/2016	SmPC	
IB/0002	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/04/2016	22/09/2016	SmPC and PL	
II/0001	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	21/04/2016	n/a		