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Swiss Summary of the Risk Management Plan (RMP) for BLINCYTO® (Blinatumomab)

RMP Summary: Version 9, August 2024
EU RMP: Version 18.0, 20 December 2023 and Switzerland-specific Annex to the EU RMP Version 1.0, 17 June 2024

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of BLINCYTO® is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of BLINCYTO® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

AMGEN Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of BLINCYTO®.

Overview of disease epidemiology

Blincyto is indicated for the treatment of patients with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL).
Blincyto is indicated for the treatment of patients with Philadelphia chromosome positive relapsed or refractory B-precursor ALL with resistance or intolerance to prior therapy including tyrosine kinase inhibitors (TKIs).
Blincyto can be used in patients with B-precursor-ALL in complete remission with MRD (minimal residual disease) ≥0.1%
Blincyto can be used for paediatric and adult patients with Philadelphia chromosome-negative and CD19-positive B-cell precursor ALL (acute lymphoblastic leukaemia) in the consolidation phase

It contains blinatumomab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Blincyto's benefits can be found in Blincyto's EPAR, including in its plain-language summary, available on the European Medicine's Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/blincyto and under the Swiss webpage:
https://www.swissmedicinfo.ch/

Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Blincyto, together with measures to minimize such risks and the proposed studies for learning more about Blincyto's risks, are outlined below.
Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.
In the case of Blincyto, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.
In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
If important information that may affect the safe use of Blincyto is not yet available, it is listed under "missing information" below.

List of Important Risks and Missing Information

Important risks of Blincyto are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Blincyto.
Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS) Opportunistic infections Cytokine release syndrome Medication errors
Important potential risks Missing information	Hematopoietic stem cell transplantation-related toxicity in children Use in patients after recent HSCT Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) Recent or concomitant treatment with other immunotherapy Long-term safety and efficacy Development impairment in children including neurological, endocrine, and immune system Subsequent relapse of leukemia in children including in the central nervous system Long-term toxicity in children Secondary malignant formation in children

HSCT = hematopoietic stem cell transplantation

Summary of Important Risks

Important identified risk: Neurologic events	
Evidence for linking the risk to the medicine	This risk was identified in an open-label, multicenter, phase 1 study, an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting.
Risk factors and risk groups	Elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical trials.
Risk minimization measures	Routine risk minimization measures • To be found in relevant sections of product information Additional risk minimization measures: • Educational materials for physicians, nurses, pharmacists and patients (including caregivers) and patient alert card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 See *Postauthorization Development Plan* of this summary for an overview

Important identified risk: Opportunistic infections	
Evidence for linking the risk to the medicine	This risk was identified in an open-label, multicenter, phase 1 study, an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting.
Risk factors and risk groups	Immunocompromised patients, including patients with active leukemia, are at risk for opportunistic infections.
Risk minimization measures	Routine risk minimization measures • To be found in relevant sections of product information Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational Patient Study 20150136 See *Postauthorization Development Plan* of this summary for an overview

Important identified risk: Cytokine Release Syndrome	
Evidence for linking the risk to the medicine	This risk was identified in an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting.
Risk factors and risk groups	In pooled safety dataset with blinatumomab, the greatest risk of developing cytokine release syndrome was on day 2 from the start of blinatumomab treatment.
Risk minimization measures	Routine risk minimization measures • To be found in relevant sections of product information Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational Patient Study 20150136 See *Postauthorization Development Plan* of this summary for an overview

Important identified risk: Medication Errors	
Evidence for linking the risk to the medicine	This risk was identified in an open-label, multicenter, phase 2 study and a confirmatory multicenter, single-arm phase 2 study. This risk was further observed in a randomized, confirmatory, phase 3 study. These events have also been observed in the postmarketing setting.
Risk factors and risk groups	No risk factors are known.
Risk minimization measures	Routine risk minimization measures • To be found in relevant sections of product information Additional risk minimization measures: • Educational Materials for Physicians, Pharmacists, Nurses, and Patients (Including Caregivers); and patient alert card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 See *Postauthorization Development Plan* of this summary for an overview

Important potential risk: Hematopoietic Stem Cell transplantation-related Toxicity in Children	
Evidence for linking the risk to the medicine	This potential risk was identified in the clinical trial setting. These events have been reported in the postmarketing setting.
Risk factors and risk groups	None currently identified
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20180130 See *Postauthorization Development Plan* of this summary for an overview

Missing Information: Use in Patients After Recent Hematopoietic Stem Cell Transplantation	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 See *Postauthorization Development Plan* of this summary for an overview

Missing Information: Recent or Concomitant Treatment With Other Anti-Cancer Therapies (Including Radiotherapy)	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 See *Postauthorization Development Plan* of this summary for an overview

Missing Information: Recent or Concomitant Treatment With Other Immunotherapy	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 See *Postauthorization Development Plan* of this summary for an overview

Missing Information: Long-term Safety and Efficacy	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational patient Study 20150136 • An open-label, controlled Study 20120215 • Observational cohort Study 20170610 • Observational cohort Study 20180130 See *Postauthorization Development Plan* of this summary for an overview

Missing Information: Development Impairment in Children Including Neurological, Endocrine, and Immune System	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational cohort Study 20180130 See *Postauthorization Development Plan* of this summary for an overview

Missing Information: Subsequent Relapse of Leukemia in Children Including in the Central Nervous System	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational cohort Study 20180130 See *Postauthorization Development Plan* of this summary for an overview

Missing Information: Long-term Toxicity in Children	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • An open-label, controlled Study 20120215 • Observational cohort Study 20170610 • Observational cohort Study 20180130 See *Postauthorization Development Plan* of this summary for an overview

Missing Information: Secondary malignant formation in children	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational cohort Study 20180130 See *Postauthorization Development Plan* of this summary for an overview

Postauthorization Development Plan

Studies Which Are Conditions of the Marketing Authorization

Study Short Name	Purpose of the Study
Study 20150136: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices Category 1	• To characterize the safety profile of blinatumomab in routine clinical practice in countries in the Europe by characterizing specific adverse events (neurological events and opportunistic infections) • To estimate the frequency and types of blinatumomab medication errors identified in patient charts
Study 20180130: Evaluation of long-term safety in pediatric patients with B-precursor ALL who have been treated with either blinatumomab or chemotherapy followed by HSCT transplantation. Category 1	• To estimate incidence of neuropsychomotor developmental impairment, endocrine impairment, neurological impairment, and immune system impairment (including auto-immune disorders and vaccine failure)

Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study 20170610: Overall survival of adverse events in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: induction with blinatumomab vs chemotherapy - an analysis of the Center for International Blood and Marrow Transplant Research Database	Primary objective: • Describe 100-day and mortality • Estimate the incidence of graft versus host disease (GVHD) (acute and chronic) <u>Safety concerns addressed:</u> • Long-term safety and efficacy
Study 20120215: A randomized, open-label, controlled phase 3 adaptive trial to investigate the efficacy, safety, and tolerability of the bi-specific T-cell engager (BiTE®) antibody blinatumomab as consolidation therapy versus conventional chemotherapy in pediatric patients with high-risk first relapse of B-precursor acute lymphoblastic leukemia (ALL)	Primary objective: • To evaluate EFS in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm <u>Safety concern addressed:</u> • Long-term safety and efficacy

Overview of the Switzerland-Specific Annex

The Switzerland-specific annex presents the differences to the blinatumomab EU RMP v18.0 relating to the indication for blinatumomab in Switzerland and the important identified risk of neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS).

New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Important Identified Risks		
Neurologic events	Important identified risk of 'neurologic events' was updated to 'neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS).'	In response to the evolving knowledge and revised classification of neurologic events occurring with T-cell targeting therapy, ICANS has been described as a syndrome of neurologic events that occur with these therapies. The grading of ICANS includes the assessment of the Immune Effector Cell-associated Encephalopathy (ICE) score along with clinical signs and symptoms. Although the ICE score was not systematically collected during clinical studies, events indicative of ICANS were observed both in clinical studies and postmarketing settings.

Additional Risk Minimization Measures

In contrast to EU RMP v17.0, AMGEN Switzerland AG proposes to retain all additional risk minimization measures. These include educational materials for pharmacists, physicians, nurses, and patients (including caregivers) and the patient alert card.

The difference to the proposed additional risk minimization measures compared with EU RMP v18.0 is stated below:

- The additional risk minimization measures (educational materials for pharmacists, physicians, nurses, and patients [including caregivers] and the patient alert card) were updated to include immune effector cell-associated neurotoxicity syndrome (ICANS) as part of the important identified risk of neurologic events.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Version	Approval Date Procedure	Change
1	24 September 2014 EMEA/H/C/003731	Important Identified Risks: • Neurologic events • Infections • Cytokine release syndrome • Infusion reactions • Tumor lysis syndrome • Capillary leak syndrome • Elevated liver enzymes • Medication errors • Febrile neutropenia and neutropenia • Decreased immunoglobulin Important Potential Risks: • Off-label use • Leukoencephalopathy Missing Information: • Risks during pregnancy and breastfeeding • Use in pediatric and adolescent patients • Use in patients with renal impairment • Use in patients with ethnic differences • Use in patients with history of relevant CNS pathology • Use in patients with active uncontrolled infections **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
1.1	07 May 2015 EMEA/H/C/003731	**Safety Concerns** • Leukoencephalopathy was renamed to leukoencephalopathy (including PML) • Use in patients with ethnic differences was renamed Use in patients with ethnic difference due to lack of data • Use in patients with history of relevant CNS pathology was renamed to Use in patients with active or history of CNS pathology including patients with active ALL in CNS Important Potential Risks: The following important potential risks were added: • Thromboembolic events (including disseminated intravascular coagulation) • Immunogenicity • Worsening of CNS events in patients with CNS pathology The following missing information was added as an important potential risk: • Worsening of hepatic impairment in patients with hepatic impairment

Version	Approval Date Procedure	Change
1.1 (continued)		Missing Information: The following missing information was added: • Use in elderly • Use in patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus • Use in patients after recent HSCT • Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy) • Recent or concomitant treatment with other immunotherapy • Effects on fertility • Long-term safety The missing information of risks during pregnancy and lactation was renamed to use in pregnancy and lactation **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
1.2	13 August 2015 EMEA/H/C/003731	**Safety Concerns** Use in patients with ethnic difference due to lack of data was renamed to Use in patients with ethnic differences Important Potential Risks: • Worsening of CNS events in patients with CNS pathology was removed as an important potential risk • Use in patients with active or a history of CNS pathology including patients with ALL in CNS was added an important potential risk • B-cell depletion and risk of infections with live virus vaccination in infants exposed in utero to Blinatumomab added as an important potential risk Missing Information: • Use in patients with active or history of CNS pathology including patients with active ALL in CNS was removed from missing information **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Removed educational material as an additional risk minimization measure for the important identified risk of infections

Version	Approval Date Procedure	Change
2.0	25 September 2015 EMEA/H/C/003731/0000	**Safety Concerns** • Patients who are breastfeeding added as a contraindication Important Potential Risks: • Important potential risk of Use in patients with active or a history of CNS pathology including patients with ALL in CNS renamed to Use in patients with active or a history of high-risk CNS pathology including patients with untreated ALL in CNS • Important potential risk of B-cell depletion and risk of infections with live virus vaccination in infants exposed in utero to blinatumomab renamed to Hematological disorders in newborn exposed in utero to blinatumomab (particularly B-cell depletion and risk of infections in case of vaccination with live virus vaccines) **Pharmacovigilance Plan** • Study 20150136 changed from a category 2 to a category 1 study • Study 20150136 added as a pharmacovigilance activity for immunogenicity • Study 00103311 added as a pharmacovigilance activity for all important identified risks, selected important potential risks, and missing information of long-term safety **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
3.1	19 September 2016 EMEA/H/C/003731/IB/0007	**Safety Concerns** • No change **Pharmacovigilance Plan** • Milestone dates amended for the Category 3 Pharmacovigilance Activities: Study 20150228 and for Study 20150163 **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
3.2	21 December 2016 EMEA/H/C/003731/IB/0007	**Safety Concerns** • No change **Pharmacovigilance Plan** • Milestone date updated for Study 20150136 **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable **Other Changes** • Updated postmarketing data

Version	Approval Date Procedure	Change
4.0	21 February 2017 EMEA/H/C/003731/II/0011	**Safety Concerns** • No change **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable **Other Changes** • Updated indication to include MRD positive B-cell precursor ALL
4.1	29 September 2017 EMEA/H/C/003731/II/0011	**Safety Concerns** • Removed data from Study 0010331 • Added Adult R/R Ph-ALL data **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
4.2	12 February 2018 EMEA/H/C/003731/II/0011	**Safety Concerns** • No change **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Updated language in Important Risk Minimization Measures Information for Physicians of Annex 11 as per SmPC update **Other Changes** • Updated language in Part I. Product Overview as per SmPC update
4.3	14 June 2018 EMEA/H/C/003731/II/0011	**Safety Concerns** Missing Information: • Updated missing information: Replaced “Long-term Safety” with “Long-term safety and efficacy” **Pharmacovigilance Plan** • Study 20170610 which was added to the EU RMP as a category 3 study during variation EMEA/H/C/003731/II/009 has been amended to extend the long-term follow-up period to 10 years • Study 20180138 which was added to the EU RMP as category 3 study during variation EMEA/H/C/003731/II/009 **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable

Version	Approval Date Procedure	Change
5.0	28 April 2017 Variation withdrawn	**Safety Concerns** Important Identified Risks: • Added language regarding cranial nerve disorders to the important identified risk of neurologic risks **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
6.0	19 June 2017 EMEA/H/C/003731/II/0018	**Safety Concerns** Missing Information: • Use in pediatric and adolescent patients was removed as missing information **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable **Other Changes** • Updated indication to include pediatric population
6.1	04 January 2018 EMEA/H/C/003731/II/0018	**Safety Concerns** Missing Information • Updated risk of thromboembolic events (including DIC) to include data regarding pediatric population **Pharmacovigilance Plan** • Milestone date was updated for Study 20150228 **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
6.2	08 May 2018 EMEA/H/C/003731/II/0018	**Safety Concerns** • No change **Pharmacovigilance Plan** • Removed Study 00103311/TOWER study as a pharmacovigilance activity • Added a category 3 pharmacovigilance activity (Study 20180130) - an ongoing observational study to perform long-term follow-up (ie, for up to 12 years) for subjects who enroll into a randomized, controlled study (20120215). **Postauthorization Efficacy Plan** • Removed Study 00103311/TOWER study as a postauthorization efficacy study as this study has been completed **Risk Minimization Measures** • Not applicable

Version	Approval Date Procedure	Change
6.3	24 July 2018 EMEA/H/C/00373/II/0018	**Safety Concerns** Important potential risk: • Added hematopoietic stem cell transplantation-related toxicity in children Missing information: • Added development impairment in children including neurological, endocrine, and immune system • Added subsequent relapse of leukemia in children including in the central nervous system • Added long-term toxicity in children • Added secondary malignant formation in children **Pharmacovigilance Plan** • Study 20180130 was reclassified from a category 3 to a category 1 pharmacovigilance activity. • Added Study 20130320, a multicenter, open-label, single-arm expanded access protocol for the treatment of pediatric and adolescent subjects with B-precursor ALL with long-term follow-up until subjects are 18 years old, as a category 3 pharmacovigilance activity. • Replaced pediatric patients with long-term safety as the safety concern addressed for Study 20120215. **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
7.0	22 December 2017 EMEA/H/C/003731/II/0009	**Safety Concerns** Missing Information: • Updated missing information: Replaced “Long-term Safety” with “Long-term safety and efficacy” **Pharmacovigilance Plan** • Study 20170610 was added as a category 3 pharmacovigilance activity for missing information of long-term safety and efficacy • Added a category 3 pharmacovigilance activity (a retrospective study to determine follow-up overall survival of subjects with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab versus standard of care chemotherapy in the phase 3 open-label, randomized Study 00103311/TOWER study) for missing information of long-term safety and efficacy **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
7.1	22 March 2018 EMEA/H/C/003731/II/0009	**Safety Concerns** • No change **Pharmacovigilance Plan** • Added 3-year interim analysis CSR date of Q2 2022 for Study 20170610 **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable
8.0	26 July 2018 EMEA/H/C/003731/II/0018	Merged Versions 6.3 and 7.1

Version	Approval Date Procedure	Change
9.0	14 November 2018 EMEA/H/C/003731/II/0011	**Safety Concerns** • Not applicable **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Added 2 postauthorization efficacy Studies E1910 and AALL1331 **Risk Minimization Measures** • Not applicable **Other Changes** • Added MRD indication as per Version 4.3 • Updated frequency, seriousness/outcomes, and severity/nature of risk as per Version 4.3
9.1	15 November 2018 EMEA/H/C/003731/II/0011	**Safety Concerns** • Not applicable **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Removed 2 postauthorization efficacy Studies E1910 and AALL1331 as per EMA request **Risk Minimization Measures** • Not applicable
10.0	Submitted within: EMEA/H/C/003731/II/0030 RMP date: 24 June 2019	**Safety Concerns** • Not applicable **Pharmacovigilance Plan** • Removed completed Study MT103-211 • Updated milestone dates for Study 20170610 **Postauthorization Efficacy Plan** • Removed completed Study 00103311/TOWER study **Risk Minimization Measures** • Not applicable **Other changes** • Updated proposed indication to include Ph^+ or remove Ph^- chromosome status
10.1	Date of RMP: 02 April 2020 Revision submitted within: EMEA/H/C/003731/II/0030	**Safety Concerns** • Not applicable **Pharmacovigilance Plan** • Not applicable **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Not applicable **Other changes** • Updated clinical trial exposure to add the numbers and patient´s characteristic for the new indications. • Updated language in the risk tables for important identified and important potential risks, and missing information. The update, in line with the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices Module V Rev 2. • Updated study titles for Studies 20170610 and 20180130. • Added a reference to Part V.2 in the risk tables and Table 55, Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern, for the safety concerns, neurological effects and medication errors.

Version	Approval Date Procedure	Change
11.0	Date of RMP: 21 August 2019 Submitted within: EMEA/H/C/003731/II/0033	**Safety Concerns** • The following important identified risks were reclassified as non-important identified risks: - infections - infusion reactions - tumor lysis syndrome - capillary leak syndrome - elevated liver enzymes - febrile neutropenia and neutropenia - decreased immunoglobulins - pancreatitis • The following important potential risks were reclassified as non-important potential risks: - off-label use - leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML]) - thromboembolic events (including disseminated intravascular coagulation [DIC]) - immunogenicity - worsening of hepatic impairment in patients with hepatic impairment - use in patients with active or a history of high-risk central nervous system (CNS) pathology including patients with untreated ALL in CNS - hematological disorders in newborn exposed in utero to blinatumomab (particularly B-cell depletion and risk of infections in case of vaccination with live virus vaccines) • The following missing information risks were removed from the safety specification: - use in pregnancy and breastfeeding - use in elderly - use in patients with renal impairment - use in patients with ethnic differences - use in patients with uncontrolled infections - use in patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus - effects on fertility **Pharmacovigilance Plan** • Updated milestone dates for Studies 20150136, 20170610, 20180138, and 20180163 • Removed completed Study 20150163 **Postauthorization Efficacy Plan** • Not applicable. **Risk Minimization Measures** • Updated safety specification as per Module SVII and Part III. **Other Changes** • Not applicable.

Version	Approval Date Procedure	Change
11.1	Date of RMP: 31 January 2020 Revision submitted within: EMEA/H/C/003731/II/0033	**Safety Concerns** • Reinserted important identified risk of infections **Pharmacovigilance Plan** • Added infections as a safety concern addressed for Study 20150136 • Updated the study title, primary objectives, and milestone date for Study 20180130 • Updated the primary objectives and milestone dates for Study 20170610 **Postauthorization Efficacy Plan** • Not applicable **Risk Minimization Measures** • Added routine risk minimization measures for the important identified risk of infections **Annexes** • Annex 3: Added the updated protocol amendments for Study 20120215, Study 20150136, Study 20180130, Study 20170610, and Study 20180138
11.2	Date of RMP: 04 May 2020 Approval date: 11 June 2020 Revision submitted within: EMEA/H/C/003731/II/0033	**Safety Concerns** • Reclassified the important identified risk of Infections to Opportunistic infections **Pharmacovigilance Plan** • Updated the milestone date for Study 20180138 **Risk Minimization Measures** • Added routine risk minimization measures for the important identified risk of opportunistic infections **Annexes** • Annex 2: Updated the milestone date for Study 20180138 • Annex 3: Added the updated protocol amendments for Study 20150136
12.0	Date of RMP: 31 July 2020 Consolidated version submitted within EMEA/H/C/003731/II/0030	Consolidated the EMA approved blinatumomab EU RMP version 11.2 submitted within procedure EMEA/H/C/003731/II/0033 and the blinatumomab EU RMP version 10.2 currently under evaluation within procedure EMEA/H/C/003731/II/0030.
12.1	Date of RMP: 27 October 2020 Revision submitted within EMEA/H/C/003731/II/0030	Aligned the RMP with the indication from the final SmPC

Version	Approval Date Procedure	Change
13.0	Date of RMP: 22 September 2020 Submitted within EMEA/H/C/003731/ II/0038	**Safety Concerns** • Not applicable **Pharmacovigilance Plan** • Removed completed Study 20150228 and Study 20130320 • Updated the objectives and milestone date for Study 20150136 • Updated the study status for Study 20180138 **Risk Minimization Measures** • Removed completed Study 20150228 and Study 20130320 as an additional pharmacovigilance activity from the summary table of pharmacovigilance activities and risk minimization activities by safety concern, where applicable. **Annexes** • Annex 2: - Removed completed Study 20150228 and Study 20130320 as ongoing studies from the pharmacovigilance plan and added to table of completed studies from the pharmacovigilance plan - Updated the objectives and milestone date for Study 20150136 - Updated the study status for Study 20180138 • Annex 3: - Added the updated protocol amendment for Study 20150136 - Removed protocols for Study 20150228 and Study 20130320
13.1	Date of RMP: 04 March 2021 Revision submitted within EMEA/H/C/00373 1/II/0038	Consolidated the EMA approved blinatumomab EU RMP version 12.1 submitted within procedure EMEA/H/C/003731/II/0030 with this RMP version 13.1. **Safety Concerns** • Not applicable **Pharmacovigilance Plan** • Updated the milestone date for Study 20180130 • Updated Section III.2 to align the studies with Section III.3 **Risk Minimization Measures** • Removed completed Study 20150163 and Study 20150228 from the plans to evaluate the effectiveness of the additional risk minimization measures • Updated the evaluation of the effectiveness of the risk minimization activities **Annexes** • Annex 2: Updated the milestone date for Study 20180130 • Annex 3: Added the updated protocol amendment for Study 20180138

Version	Approval Date Procedure	Change
14.0	Date of RMP: 04 February 2021 Approval date: 31 March 2021 Submitted within: EMEA/H/C/00373 1/IB/0041	**Pharmacovigilance Plan** • Removed completed Study 20180138 from the pharmacovigilance plan **Risk Minimization Measures** • Removed completed Study 20180138 as an additional pharmacovigilance activity from the summary table of pharmacovigilance activities and risk minimization activities by safety concern, where applicable **Annexes** • Annex 2: Removed completed Study 20180138 as ongoing studies from the pharmacovigilance plan and added to table of completed studies from the pharmacovigilance plan • Annex 3: Added the updated protocol amendment details for 20180138 • Annex 6: Updated the details of the additional risk minimization materials
15.0	Date of RMP: 05 May 2021 Revision submitted within: EMEA/H/C/00373 1/II/0038 Approval date: 20 May 2021	Consolidated the current EMA-approved blinatumomab EU RMP version 14.0, which was submitted within procedure EMEA/H/C/003731/IB/0041, and the blinatumomab EU RMP version 13.1, which was reviewed and determined to be acceptable within procedure EMEA/H/C/003731/II/0038.
16.0	Date of RMP: 26 September 2022	**Safety concerns** • Updated the study duration, enrolment period, and the maximum follow-up period for Study 20150136 **Pharmacovigilance Plan** • Updated 20150136 study details to include CRS as primary endpoint to align with the study protocol. **Annexes** • Annex 3: Added the updated protocol amendments for 20150136 and 20120215
17.0	Date of RMP: 25 October 2023 Submitted within: EMEA/H/C/003731/II/ 0054	**Safety concerns** • Updated important identified risk of 'neurologic events' to 'neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS).' **Pharmacovigilance Plan** • Removed additional risk minimization measures to: - Remove the educational materials for pharmacists, physicians, and nurses - Update the educational material for patients and caregivers and the patient alert card to include ICANS with the risk of neurologic events **Annexes** • Annex 2: Updated category 3 Study 20120215 from ongoing to completed. • Annex 3: Removed protocol for completed • Study 20120215 and added updated protocol amendments for Studies 20180130 and 20150136 • Annex 6: Removed the educational materials for pharmacists, physicians, and nurses, and updated the educational material for patients and caregivers and the patient alert card to include ICANS with the risk of neurologic events.

Version	Approval Date Procedure	Change
18.0	Date of RMP: 20 December 2023	**Safety concerns** • Not applicable **Pharmacovigilance Plan** • Not applicable **Risk Minimization Measures** • Not applicable **Annexes** • Not applicable **Other changes** • Expanded the indication to include the treatment of patients with Philadelphia chromosome negative CD19-positive B-cell precursor ALL in the consolidation phase. • Updated clinical trial exposure data and frequency/severity data for important identified risks based on the latest clinical study data.

This summary was last updated in August 2024.