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Swiss Summary of the Risk Management Plan for Casgevy® (exagamglogene autotemcel [exa-cel])

Version 1.0 (dated 24 October 2024) corresponding to EU-RMP Version 1.1

Disclaimer: 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 minimise them.

The RMP summary of Casgevy® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary may differ from the "Arzneimittelinformation/ Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Casgevy® in Switzerland, is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedic.ch), approved and authorised by Swissmedic.

Vertex Pharmaceutics (CH) GmbH is fully responsible for the accuracy and correctness of the content of the published RMP summary of Casgevy®.

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SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR CASGEVY (EXAGAMGLOGENE-AUTOTEMCEL)

This is a summary of the risk management plan (RMP) for CASGEVY. The RMP details important risks of CASGEVY, how these risks can be minimised, and how more information will be obtained about CASGEVY's risks and uncertainties (missing information).

CASGEVY's Summary of product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how CASGEVY should be used.

This summary of the RMP for CASGEVY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current ones will be included in updates of CASGEVY's RMP.

I. The medicine and what it is used for

CASGEVY is authorised for the treatment of transfusion dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available (see SmPC for the full indication). CASGEVY is also authorised for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available (see SmPC for the full indication).

CASGEVY is a one-time gene therapy. It is made specifically for each patient, using the patient's own blood stem cells. Blood stem cells are cells that can turn into other blood cells including red cells, white cells, and platelets. The cells are taken from the patient, then are genetically modified and they are given back to the same patient as a stem cell transplant.

Further information about the evaluation of CASGEVY's benefits can be found in CASGEVY's EPAR, including its plain-language summary, available on the EMA website under the medicine's webpage: https://www.ema.europa.eu/en/documents/rmp/casgevy-epar-risk-management-plan_en.pdf.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of CASGEVY, together with measures to minimise such risks and the proposed studies for learning more about CASGEVY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

If important information that may affect the safe use of CASGEVY, it is listed under 'missing information' below.

II. A List of important risks and missing information

Important risks of CASGEVY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 CASGEVY. 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 (e.g., on the long-term follow up of the medicine).

List of important risks and missing information	
Important identified risks	• Delayed platelet engraftment
Important potential risks	• Neutrophil engraftment failure • Gene editing-related oncogenesis
Missing information	• Long-term effects • Pregnancy and lactation • Use in patients >35 years of age

II.B Summary of important risks

Delayed platelet engraftment (Important identified risk)	
Evidence for linking the risk to the medicine	In the pivotal Phase 1/2/3 clinical study in subjects 12 to 35 years of age with TDT (Study 111) and SCD (Study 121), median time to platelet engraftment after CASGEVY infusion was comparatively longer than reported in allogeneic HSCT; however, it was consistent with the median time reported in other genetic therapies involving HSCT. There was no association observed between bleeding AEs and time to platelet engraftment after CASGEVY infusion. However, thrombocytopenia following myeloablative conditioning is a risk factor for serious bleeding-related complications, with the highest risk occurring prior to platelet engraftment. As such, delayed platelet engraftment is considered and important identified risk.
Risk factors and risk groups	Following infusion with CASGEVY, subjects with TDT without a spleen (i.e., splenectomised) had an earlier median time to platelet engraftment than subjects with an intact spleen. This finding is similar to data from allogenic HSCT and other genetic therapies for β-thalassemia major.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.1, 4.2, and 4.4: • Indication for treatment of patients with β-hemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of CASGEVY must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Recommendations for monitoring platelet counts and managing symptoms of bleeding are provided in SmPC Section 4.4. PL Sections 2 and 4:

	• Advice to on how to identify symptoms of bleeding and when to contact the doctor is given in PL Sections 2 and 4. Restricted prescription medicine <u>Additional risk minimisation measures:</u> • Guide for HCPs • Patient Card • Guide for Patients/Carers
Additional pharmacovigilance activities	• Study 101[a] (PASS) • HCP Survey (PASS) *Efficacy studies that will provide relevant safety results:* • Study 111 in subjects with TDT ages 12 to 35 years • Study 121 in subjects with SCD ages 12 to 35 years • Study 151 in subjects with SCD ages 2 to 11 years • Study 161 in subjects with TDT or SCD ages 12 to 35 years • Study 171 in subjects with SCD ages 12 to 35 years See Section II.C of this summary for an overview of the post-authorisation development plan.
Neutrophil engraftment failure (Important potential risk)	
Evidence for linking the risk to the medicine	Neutrophil engraftment failure is considered an important potential risk because of the possibility for neutrophil engraftment failure to be an outcome of any myeloablation and bone marrow transplantation. Failure to achieve neutrophil engraftment would require a subsequent HSCT procedure with unmodified rescue $CD34^+$ stem cells, thereby negating beneficial effects of CASGEVY gene therapy. However, in the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) and SCD (Study 121), there was no evidence of neutrophil engraftment failure after CASGEVY infusion and this risk is considered potential.
Risk factors and risk groups	As no subjects with TDT or SCD failed to achieve neutrophil engraftment following CASGEVY infusion, no risk factors or risk groups were identified in the clinical programme.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.1, 4.2, and 4.4: • Indication for treatment of patients with β-hemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of CASGEVY must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Collection of unmodified rescue $CD34^+$ stem cells is required prior to myeloablative conditioning and infusion with CASGEVY, as outlined in SmPC Section 4.2. • Guidance for administering unmodified rescue cells in the event of neutrophil engraftment failure is provided in SmPC Sections 4.2 and 4.4. • Recommendations for monitoring neutrophil counts and managing infections are provided in SmPC Section 4.4. PL Sections 2 and 4: • Information on what to expect if engraftment fails is provided in PL Section 2. • Advice on how to identify symptoms of infection and when to contact the doctor is given in PL Sections 2 and 4. Restricted prescription medicine

	Additional risk minimisation measures: • Guide for HCPs • Patient Card • Guide for Patients/Carers
Additional pharmacovigilance activities	• Study 101[a] (PASS) • HCP Survey (PASS) *Efficacy studies that will provide relevant safety results:* • Study 111 in subjects with TDT ages 12 to 35 years • Study 121 in subjects with SCD ages 12 to 35 years • Study 151 in subjects with SCD ages 2 to 11 years • Study 161 in subjects with TDT or SCD ages 12 to 35 years • Study 171 in subjects with SCD ages 12 to 35 years See Section II.C of this summary for an overview of the post-authorisation development plan.
Gene editing-related oncogenesis (Important potential risk)	
Evidence for linking the risk to the medicine	Gene editing-related oncogenesis is considered an important risk as it is theoretically possible after Casgevy infusion. In the clinical programme, there have been no reports of blood cancers due to treatment with Casgevy and no potential identified in nonclinical and in silico studies; therefore, this risk is considered potential.
Risk factors and risk groups	There have been no reports of gene editing-related oncogenesis in follow-up of up to 4 years after Casgevy infusion; therefore, no risk factors or risk groups were identified in the clinical programme.
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Section 4.4 • Description that there have been no cases of myelodysplasia, leukaemia, or lymphoma from the clinical studies • As a theoretical risk, recommend monitoring at least annually (including complete blood count) for 15 years after treatment. Restricted prescription medicine Additional Risk Minimisation Measures • Guide for HCPs • Patient Card • Guide for Patients/Carers
Additional pharmacovigilance activities	• Study 101[a] (PASS) • HCP Survey (PASS) *Efficacy studies that will provide relevant safety results:* • Study 131 Long term follow-up study in subjects with TDT and SCD See Section II.C of this summary for an overview of the post-authorisation development plan.
Long-term effects (Missing information)	
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Section 4.4: • Recommendation for long-term follow up is provided in SmPC Section 4.4. PL Section 2: • Expectations for long-term monitoring are described in PL Section 2.

	Restricted prescription medicine Additional Risk Minimisation Measures • Guide for HCPs • Guide for Patients/Carers
Additional pharmacovigilance activities	• Study 101[a] (PASS) • HCP Survey (PASS) *Efficacy studies that will provide relevant safety results:* • Study 131 Long term follow-up study in subjects with TDT and SCD See Section II.C of this summary for an overview of the post-authorisation development plan.
Pregnancy and lactation (Missing information)	
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Section 4.6: • Recommendations for contraception use, breastfeeding, and pregnancy, including a negative pregnancy test prior to the start of any treatment, are provided in SmPC Section 4.6. • CASGEVY must not be administered during pregnancy or breastfeeding due to risks associated with myeloablative conditioning, as stated in SmPC Section 4.6. PL Section 2: • Expectations for use of contraception, pregnancy testing, and breastfeeding are described in PL Section 2. • Advice for talking to the doctor prior to starting treatment is given in PL Section 2. Restricted prescription medicine Additional Risk Minimisation Measures None
Additional pharmacovigilance activities	• Study 101[a] (PASS; pregnancy outcomes) *Efficacy studies that will provide relevant safety results:* • Study 131 Long term follow-up study in subjects with TDT and SCD See Section II.C of this summary for an overview of the post-authorisation development plan.
• **Use in patients >35 years of age (Missing information)**	
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Section 4.2 • Recommendation to consider the benefits of treatment against the risks of HSCT is provided in SmPC Section 4.2. Restricted prescription medicine Additional Risk Minimisation Measures None
Additional pharmacovigilance activities	• Study 101 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.

AE: adverse event; HSCT: haematopoietic stem cell transplant; PASS: post-authorisation safety study
PL: Package Leaflet; SCD: sickle cell disease; SmPC: Summary of Product Characteristics;
TDT: transfusion-dependent β-thalassemia

[a] Study 101 (PASS) Progress Reports 1, 2, and 3 and Interim Report 1 will be provided as a special obligation in the context of a conditional MA.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Study 101: Post-authorisation safety study *(PASS)*
Purpose of the study: To evaluate the long-term safety and effectiveness outcomes in patients who received CASGEVY for treatment of TDT or SCD in comparison to patients receiving allogenic HSCT

Study 111: Study in subjects with TDT ages 12 to 35 years
Purpose of the study: To evaluate the safety and efficacy of CASGEVY in subjects with TDT

Study 121: Study in subjects with SCD ages 12 to 35 years
Purpose of the study: To evaluate the safety and efficacy of CASGEVY in subjects with SCD

Study 131: Long-term follow-up study in subjects with TDT and SCD
Purpose of the study: To evaluate the long-term safety and efficacy for 15 years in patients who received CASGEVY for treatment of TDT or SCD

Study 151: Study in subjects with SCD ages 2 to 11 years
Purpose of study: To evaluate the safety and efficacy of CASGEVY in paediatric subjects with SCD

Study 161: Study in subjects with TDT or SCD ages 12 to 35 years
Purpose of study: To evaluate the foetal hemoglobin levels over time, safety, and efficacy of CASGEVY in subjects with TDT or SCD

Study 171: Study in subjects with SCD ages 12 to 35 years
Purpose of study: To evaluate the safety and efficacy of CASGEVY in subjects with SCD, βS/βC genotype

II.C.2 Other studies in post-authorisation development plan

Healthcare Professional (HCP) Survey to assess the effectiveness of the additional risk minimisation measures (aRMMs) for exagamglogene autotemcel (Casgevy) *(PASS)*
Purpose of the study: To assess the HCPs' understanding of the important safety information detailed in the Guide for HCPs, the HCPs' awareness of the aRMM tools, and the HCPs' utilisation of aRMM tools (behaviour)