CSL Behring

Hemgenix

etranacogene dezaparvovec
INN: AAV5-hFIXco-Padua

Swiss Summary to the Risk Management Plan

Version number of RMP: 1.0

Marketing Autorisation Holder: CSL Behring AG

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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 Hemgenix 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 Hemgenix in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. CSL Behring Lengnau AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Hemgenix.

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The medicine and what it is used for

Hemgenix is authorized for the treatment of severe and moderately severe Hemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors. It contains etranacogene dezaparvovec as the active substance and it is administered as a single intravenous infusion.

Further information about the evaluation of Hemgenix's benefits can be found in Hemgenix's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page.

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

Important risks of Hemgenix, together with measures to minimize such risks and the proposed studies for learning more about Hemgenix'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 HCPs.
- 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 patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report 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 Hemgenix is not yet available, it is listed under 'missing information' below.

List of important risks and missing information

Important risks of Hemgenix 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 Hemgenix. 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	• Hepatotoxicity • Infusion reactions (including hypersensitivity)
Important potential risks	• Risk of malignancy in relation to vector integration in the DNA of body cells • Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid • Thromboembolic events • Germline transmission • Transmission to third parties (horizontal transmission) • Development of FIX inhibitors
Missing information	• Use in patients with severe hepatic impairment • Long-term effect • Use in female patients

Summary of important risks

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	In the majority mild and transient transaminitis events were observed in the preclinical studies and during the clinical development program of etranacogene dezaparvovec. Furthermore, liver function abnormalities have been reported in clinical trials results published in the literature and investigating IV administration of a liver directed AAV vector (Rangarajan et al, 2017; Nathwani et al, 2011; Nathwani et al, 2014; Nathwani et al, 2018; George, 2017; Manno et al, 2006).
Risk factors and risk groups	Common causative/risk factors for hepatotoxicity include: • Elderly patients are at increased risk of hepatic injury due to reduced blood flow to the liver • Drug-drug interactions • Alcohol abuse in patients with cirrhotic liver changes • Concomitant use of hepatotoxic medications
Risk minimization measures	<u>Routine risk minimization measures:</u> • SmPC sections 4.2, 4.4, 4.8 • Legal status: Prescription only product <u>Additional risk minimization measures:</u> Health care professional guide, patient guide and patient card

Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk: Infusion reactions (including hypersensitivity)	
Evidence for linking the risk to the medicine	Mild to moderate infusion-related reactions were observed the clinical studies with etranacogene dezaparvovec. In the scientific literature, a small number of infusion-related reactions after intravenous infusion of AAV5-based gene therapy has been reported. These events were successfully mitigated by slowing or pausing the infusion and administering medications such as antihistamines, antipyretics or glycocorticoids (Ozelo et al, 2022).
Risk factors and risk groups	No specific risk factors are known. However, patients with high levels of preexisting neutralizing antibodies against AAV5 might be more likely to experience infusion reactions.
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4, 4.8 • Legal status: Prescription only product Additional risk minimization measures: None
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Risk of malignancy in relation to vector integration in the DNA of body cells	
Evidence for linking the risk to the medicine	Chromosomal integration of vectors is considered to present a risk for malignant transformation of cells due to insertional mutagenesis and activation, inactivation or alteration of host cell genes. Therefore, viral vectors mediating transfer of their genetic material into the cell nucleus present a risk can have a high risk for delayed adverse reactions (CHMP, 2009). One case of hepatocellular carcinoma was observed in the etranacogene dezaparvovec clinical development program in an elderly subject with multiple risk factors (HCV, HBV, age > 50, alcohol use, family history of cancer). The event was considered as unlikely related to the etranacogene dezaparvovec treatment upon review of detailed genetic and insertion site analysis.

Risk factors and risk groups	The following have been described as risk factors for the development of HCC (Llovet et al, 2021): • Infection with Hepatitis B and/or Hepatitis C • Chronic alcohol consumption • Advanced fibrosis • Cirrhosis • Non-alcoholic steatohepatitis (NASH), associated with diabetes mellitus, or obesity • Non-alcoholic fatty liver disease • Advanced age • Male gender
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2, 4.4 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid	
Evidence for linking the risk to the medicine	The etranacogene dezaparvovec clinical studies suggest that although AAV5 neutralizing antibodies were prevalent in humans, the absolute levels at which they were present may not have been adequate to significantly impact the infused dose of etranacogene dezaparvovec in the majority of patients. All patients receiving Hemgenix will develop NAbs against AAV5 in the weeks after administration. However, by that time the vector DNA will have been delivered to the nucleus of the cell where it will direct transgene expression. As such, production of hFIX-Padua is not expected to be impacted by the generation of the anti-capsid humoral immune response.
Risk factors and risk groups	There is a lack of data in patients with neutralizing anti-AAV5 antibodies above 1:678. Therefore, these patients could be considered at higher risk, due to the limited clinical experience.

Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4, 5.1 • Legal status: Prescription only product Additional risk minimization measures: None
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Thromboembolic events	
Evidence for linking the risk to the medicine	Thromboembolism (e.g., pulmonary embolism, venous thrombosis, and arterial thrombosis) has occurred when using Factor IX-containing concentrate. One event of pulmonary thrombi was observed in the pre-clinical studies of etranacogene dezaparvovec. Additionally, in the clinical development program of etranacogene dezaparvovec, four events potentially relating to a thromboembolic episode were reported.
Risk factors and risk groups	Additional risks factors for TEEs in the targeted population are the same in the general population and include (Geerts et al, 2008; Previtali et al, 2011): Venous thrombosis risks • Pregnancy • Hormone replacement therapy • Surgery • Immobilization • Trauma • Cancer Arterial thrombosis risks • Smoking • Hypertension • Hypercholesterolemia • Peripheral vascular disease • Diabetes • Obesity
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2, 4.4 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001

	See section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Germline transmission	
Evidence for linking the risk to the medicine	The question whether recombinant AAV vector sequences may transduce male spermatogonial stem cells and generate vector DNA-positive mature sperm cells (i.e., vertical germline transmission) has been extensively investigated and reported in the scientific literature. Schuettrumpf et al, 2006, as well as Jakob et al, 2005; Favaro et al, 2009; Arruda et al, 2001 and Fonck et al, 2022 did not detect vector sequences in sperm derived from dozens of cumulative spermatogenesis cycles in mice or rabbits after infusion of recombinant AAV. This indicates that biodistribution to male gonadal tissues does not lead to production of sperm carrying vector DNA. Together with the aforementioned absence of a vector signal in reproductive tissue of females, this indicates an extremely low likelihood of inadvertent germ line transfer (horizontal or vertical) of etranacogene dezaparvovec in patients treated with CSL222. There is no risk of shedding of transduction competent vector particles via bodily fluids after more than a few days post infusion (Schuettrumpf, 2006; Favaro et al, 2009; Rangarajan et al, 2017; Fonck et al, 2022). Following cellular uptake of transduction competent virus particles in the immediate post-infusion period, remaining capsid bearing vector particles will be rendered transduction incompetent and removed via the development of an effective NAb response against the AAV5 capsid protein in bodily fluids (within days). All subjects in the CSL222 clinical trials have developed such an immune response within 2-3 weeks post vector infusion. This immune response is long lasting and exceeds the period during which any shedding of vector DNA is observable in trial subjects. Therefore, there is no relevant exposure risk of transduction competent AAV Particles and thus there is no prolonged relevant exposure risk of transduction to contacts. Exposure risk to close contacts in the immediate post-infusion period is further mitigated by the recommendation for a 1-year use of barrier contraception following Hemgenix administration as outlined in the Hemgenix SmPC. Based on the low level of vector DNA in semen, its presence in the seminal fluid instead of the cellular fraction of semen, the low integration potential of non-replicating rAAV vectors, and the recommendation of barrier contraception during the time when transduction competent particles are present in semen, the likelihood of horizontal germline transmission is considered negligible.
Risk factors and risk groups	In theory, an immediate effect of germline transmission is the addition of a hFIX-Padua expression cassette to the genome of progeny. Whether this addition will actually lead to the expression of hFIX-Padua protein depends on whether the vector genome will integrate in the host genome of progeny. If the vector genome remains episomal, it most likely will be lost during the many cell divisions in the development of the fetus. However, in the hypothetical situation that the complete expression cassette will be integrated, the expression of hFIXco-Padua can potentially materialize. Based on experience in the nonclinical and clinical studies the severity of overexpression of hFIX-Padua protein is considered low. However, the integration of part of the vector genome might also lead to insertional mutagenesis including its potential consequences. Women of childbearing potential and male patients, including vasectomized males, are defined as risk groups.
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4, 4.6 • Legal status: Prescription only product

	Additional risk minimization measures: Health care professional guide, patient guide and patient card.
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Transmission to third parties (horizontal transmission)	
Evidence for linking the risk to the medicine	Shedding and clearance of AAV5-hFIX-Padua were evaluated in pre-clinical and clinical studies. In Studies CSL222_2001 and CSL222_3001, clearance of vector DNA from blood was confirmed in 2/3 and 25/54 subjects, respectively, at the earliest 17 and 31.1 weeks after administration. It is anticipated that quantitative polymerase chain reaction (qPCR)-detectable etranacogene dezaparvovec DNA fragments will be present in body fluids and excreta for several weeks after administration. However, the detected vector DNA does not equate infectious vector particles. Apart from an infectious particle, it can also represent DNA from a degraded vector particle, a particle that has been taken up by a cell, or a cell that has been transduced by the vector (e.g., leukocytes or epithelial cells of the bladder). Furthermore, the development of anti-AAV5 neutralizing antibodies in the immediate post-infusion period, will render any remaining capsid-bearing vector particles in the patients' blood and seminal compartments. This immune response is long lasting and exceeds the period during which any shedding of vector DNA is observable in trial subjects. Therefore, the presence of vector DNA in body fluids and secretions is not expected to have any impact on individuals potentially exposed.
Risk factors and risk groups	The following risk groups are identified for this hypothetical risk: • Recipients of blood, organs, tissues, or cells originated from Hemgenix-treated individuals • Close contacts of patients • Laboratory staff handling patient's samples that may contain (parts of) the vector
Risk minimization measures	Routine risk minimization measures: • SmPC sections, sections 4.4 and 5.2 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card.
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk: Development of FIX inhibitors	
Evidence for linking the risk to the medicine	No subjects developed FIX inhibitors in the clinical development program of etranacogene dezaparvovec.
Risk factors and risk groups	History of FIX inhibitors and positive FIX inhibitor test at screening were exclusion criteria in the etranacogene dezaparvovec clinical development program. Subjects with at least 150 EDs of treatment with FIX protein were included in the CSL222 clinical studies. Although the likelihood of FIX inhibitors development following administration of gene therapy is very low, patients with less than 150 EDs to FIX concentrates could be considered at higher risk, due to the limited clinical experience.
Risk minimization measures	Routine risk minimization measures: • SmPC sections, sections 4.1, 4.2, 4.4, 4.8 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card.
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Use in patients with severe hepatic impairment	
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.3, 4.4, 4.5, 5.2 • Legal status: Prescription only product Additional risk minimization measures: None.
Additional pharmacovigilance activities	• Study CSL222_4001 See section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Long-term effect	
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide and patient guide.
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See section II.C of this summary for an overview of the post-authorization development plan.

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Missing information: Use in female patients	
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2, 4.6 • Legal status: Prescription only product Additional risk minimization measures: None.
Additional pharmacovigilance activities	• Study CSL222_4001 See section II.C of this summary for an overview of the post-authorization development plan.

AAV: adeno-associated virus, DNA: deoxyribonucleic acid, ED: Exposure day, (h)FIX: (human) factor IX, hFIXco Padua: gain-of-function Padua-variant of the human Factor IX, HBV: hepatitis B virus, HCC: hepatocellular carcinoma, HCV: hepatitis c virus, IV: intravenous, NAb: neutralizing antibody, qPCR: quantitative polymerase chain reaction, SmPC: summary of product characteristics, TEE: thromboembolic event

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Post-authorization development plan

Studies which are conditions of the marketing authorization

The following studies are a condition of the marketing authorization:

CSL222_4001: An observational post-authorization Long-term Follow-up Study to Characterize the Safety and Effectiveness of Hemgenix (Etranacogene Dezaparvovec) in Patients with Hemophilia B

Purpose of the study:

The purpose of this observational Study CSL222_4001 is to evaluate the long-term effectiveness and safety of Hemgenix in a larger population of adult patients with Hemophilia B treated as per the approved Hemgenix label in regions where Hemgenix is approved for use and commercialized. The study will include a cohort of patients with Hemophilia B treated with continuous FIX prophylaxis to enable interpretation of relevant safety findings in patients with Hemophilia B.

CSL222_2001: A phase 2b, open-label, single-dose, single-arm, multi-center trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5 hFIX Padua) administered to adult subjects with severe or moderately severe Hemophilia B

Purpose of the study:

The primary aim of this trial is to confirm that a single dose of 2 x 1013 gc/kg etranacogene dezaparvovec will result in factor IX activity levels of ≥5%. An objective of the trial is to assess whether observed factor IX activity levels are within an expected range, to determine if 2 x 1013 gc/kg AMT-061 is suitable from efficacy point of view for administration in the pivotal Phase 3 trial. In addition, the safety profile of etranacogene dezaparvovec will be demonstrated.

CSL222_3001: A phase 3, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIX-Padua) administered to adult subjects with severe or moderately severe Hemophilia B

Purpose of the study:

The purpose of this Phase III trial is to demonstrate the efficacy of etranacogene dezaparvovec in terms of annualized bleeding rate, to further describe its efficacy in terms of endogenous factor IX activity, and to further describe its safety profile.

Other studies in post-authorization development plan

The following additional pharmacovigilance activities are included in the post-authorization

development plan:

CSL222_3003: An Extension Study Assessing the Long-term Safety and Efficacy of Etranacogene Dezaparvovec Previously Administered to Adult Male Patients with Hemophilia B during the CSL222_2001 (CT AMT-061-01) and CSL222_3001 (CT AMT 061-02) Studies.

Purpose of the study:

This interventional long term follow-up extension study will follow adult male patients with severe or moderately severe Hemophilia B (FIX activity ≤ 2%) who previously received an infusion of AAV5 hFIXco-Padua (etranacogene dezaparvovec) in the parent studies, CSL222_2001 and CSL222_3001 with the aim to assess the long-term safety and efficacy of etranacogene dezaparvovec (6 to 15 years from the time of initial dosing).

CSL222_5001: Survey to evaluate the effectiveness of additional risk minimisation measures (aRMMs) for Hemgenix among prescribers in the EU

Purpose of the study:

CSL Behring will develop and disseminate aRMM in the form of a Guide for HCP, Patient/Caregiver Guide and a Patient Card to address the important identified risk of hepatotoxicity and the important potential risks of thromboembolic events, germline transmission, risk of malignancy in relation to vector integration in the DNA of body cells and long-term effect as per the RMP.

CSL Behring will perform this survey in order to evaluate the effectiveness of such aRMM tools.

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Summary of changes to the Swiss RMP Summary

Version	Date	Change History	Comment
01	2-Feb-2024	Initial document	Initial document, based on EU RMP Version 1.0, 14-Dec-2022