CSL Behring

Important Safety Information HEMGENIX®

Health Care Professional Guide

HEMGENIX® (etranacogene dezaparvovec)

Please read this information and the HEMGENIX® Summary of Product Characteristics (SmPC) carefully before prescribing HEMGENIX® treatment.

HEMGENIX® Health Care Professional Guide
Version 2.0
Approved by Saudi Food and Drug Authority on July-2025
MEA-HGX-0001

1 What is ETRANACOGENE DEZAPARVOVEC?

ETRANACOGENE DEZAPARVOVEC is a gene therapy medicinal product that expresses the human coagulation Factor IX. It is a non-replicating, recombinant adeno-associated virus serotype 5 (AAV5) based vector containing a codon-optimised cDNA of the human coagulation Factor IX variant R338L (FIX-Padua) gene under the control of a liver-specific promoter (LP1). Etranacogene dezaparvovec is produced in insect cells by recombinant DNA technology.

a. How does ETRANACOGENE DEZAPARVOVEC work?

Following single intravenous infusion, etranacogene dezaparvovec preferentially targets liver cells, where the vector DNA resides almost exclusively in episomal form. After transduction, etranacogene dezaparvovec directs long-term liver-specific expression of Factor IX-Padua protein. As a result, etranacogene dezaparvovec partially or completely ameliorates the deficiency of circulating Factor IX procoagulant activity in patients with Haemophilia B.

b. Indication

Etranacogene dezaparvovec is indicated for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

2 Important risk information related to the use of ETRANACOGENE DEZAPARVOVEC

a. Hepatotoxicity

Intravenous administration of a liver-directed AAV vector may potentially lead to liver transaminase elevations (transaminitis). The transaminitis is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of the gene therapy.

To mitigate the risk of potential hepatotoxicity:

- **Patient's liver health should be evaluated before administration of Etranacogene dezaparvovec and closely monitored after treatment with etranacogene dezaparvovec** (see Table 1).

- It is recommended that the hepatic function is evaluated through a multidisciplinary approach with involvement of a **hepatologist** to best adjust the monitoring to the patient's individual condition.

- It is advised that patients treated with etranacogene dezaparvovec **avoid concomitant use of hepatotoxic medication or agents as this** may reduce the efficacy of etranacogene dezaparvovec and increase the risk for more serious hepatic reactions, particularly during the first year following etranacogene dezaparvovec administration.

- Treating physicians should **ensure the availability of patients for frequent monitoring of hepatic laboratory parameters after administration of etranacogene dezaparvovec.**

Table 1. Hepatic function and Factor IX activity monitoring

	Measurements	Timeframe	Monitoring frequency[a]
Before administration Please read this information and the etranacogene dezaparvovec Summary of Product Characteristics (SmPC) carefully before prescribing etranacogene dezaparvovec treatment.	Liver function tests Recent fibrosis assessment	Within 3 months prior to infusion Within 6 months prior to infusion	Baseline measurement
After administration	Alanine aminotransferase (ALT)and Factor IX activity	First 3 months	Weekly
		Months 4 to 12 (Year 1)	Every 3 months
		Year 2	• Every 6 months for patients with Factor IX activity levels > 5 IU/dL (see Factor IX assays) • Consider more frequent monitoring in patients with Factor IX activity levels ≤ 5 IU/dL and consider the stability of Factor IX levels and evidence of bleeding.
		After Year 2	• Every 12 months for patients with Factor IX activity levels > 5 IU/dL (see Factor IX assays) • Consider more frequent monitoring in patients with factor IX activity levels ≤5 IU/dL, and consider the stability of factor IX levels and evidence of bleeding

* It is recommended (where possible) to use the same laboratory for hepatic testing at baseline and monitoring over time, particularly during the timeframe for corticosteroid treatment decision making, to minimise the impact of inter-laboratory variability.

[a] Weekly monitoring is recommended, or as clinically indicated, during corticosteroid tapering. Adjustment of the monitoring frequency may also be indicated depending on the individual situation.

- In the event of ALT increase to above the upper limit of normal, or
- In the event of ALT increase to double the patient's baseline levels

You should consider:

- A course of corticosteroid treatment to dampen the immune response (see Table 2)
- Human Factor IX activity examinations

Table 2. Recommended prednisolone treatment in response to ALT elevations

Timeline	Prednisolone oral dose (mg/day)*
Week 1	60
Week 2	40
Week 3	30
Week 4	30
Maintenance dose until ALT level returns to baseline level	20
Taper dose after ALT baseline level has been reached	Reduce daily dose by 5mg/week

*Medicinal products equivalent to prednisolone may also be used. A combined immunosuppressant regimen or the use of other immunosuppressive therapy can also be considered in case of prednisolone treatment failure or contraindication.

Follow-up monitoring of transaminases in all patients who developed liver enzyme elevations is recommended on a regular basis until liver enzymes return to baseline values.

It is further recommended to assess possible alternative causes of the ALT elevation including administration of potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise. Retesting of ALT levels within 24 to 48 hours and, if clinically indicated, performing additional tests to exclude alternative aetiologies should be considered.

b. Potential risk of thromboembolic events

Patients with Haemophilia B have, compared to the general population, a reduced potential for thromboembolic events (e.g. pulmonary thromboembolism or deep venous thrombosis) due to inborn deficiency in the clotting cascade. Alleviating symptoms of Haemophilia B by restoring Factor IX activity may expose patients to the potential risk of thromboembolism, as observed in the general non- haemophilic population.

In patients with Haemophilia B with preexisting risk factors for thromboembolic events,

such as a history of cardiovascular or cardiometabolic disease, arteriosclerosis, hypertension, diabetes, advanced age, the potential risk of thrombogenicity may be higher.

In the clinical studies with etranacogene dezaparvovec, treatment-related thromboembolic events were not reported. In addition, no supraphysiological Factor IX activity levels were observed.

c. Potential risk of malignancy as a result of vector integration

Integration site analysis was performed on liver samples from one patient treated with Etranacogene dezaparvovec in clinical studies. Samples were collected one year post-dose. Vector integration into human genomic DNA was observed in all samples.

- The clinical relevance of individual integration events is not known to date, but it is acknowledged that individual integration into human genome could potentially contribute to a risk of malignancy
- In the clinical studies, no malignancies were identified in relation to treatment with etranacogene dezaparvovec

It is recommended that **patients with preexisting risk factors for hepatocellular carcinoma** (such as hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) **undergo regular liver ultrasound screenings and are regularly monitored for alpha-fetoprotein (AFP) elevations (e.g. annually) for at least 5 years after ETRANACOGENE DEZAPARVOVEC administration.**

In the event that a malignancy occurs, the marketing authorisation holder should be contacted by the treating healthcare professional to obtain instructions on collecting patient samples for potential vector integration examination and integration site analysis.

d. Potential risk of germline and horizonal transmission of ETRANACOGENE DEZAPARVOVEC

In clinical studies, after administration of etranacogene dezaparvovec, transgene DNA was temporarily detectable in semen and blood.

To minimize the potential risk of paternal germline transmission, it is recommended that:

- Treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy **using a barrier contraception for 12 months after administration of Etranacogene dezaparvovec**
- Male patients treated with Etranacogene dezaparvovec **must not donate semen**

Experience regarding the use of Etranacogene dezaparvovec during pregnancy is not available. It is not known whether Etranacogene dezaparvovec can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Etranacogene dezaparvovec should not be used during pregnancy and is not recommended in women of childbearing potential.

To mitigate the potential risk for horizontal transmission (transmission to third parties), the **patient must not donate blood, semen or organs, tissues, and cells for transplantation.**

e. Potential risk of development of FIX inhibitors

There is no clinical experience with administration of Etranacogene dezaparvovec in patients who have or had inhibitors to Factor IX. It is not known whether or to what extent such preexisting Factor IX inhibitors may affect the safety or efficacy of Etranacogene dezaparvovec. In patients with a history of Factor IX inhibitors, ETRANACOGENE DEZAPARVOVEC treatment is not indicated.

In the clinical studies with Etranacogene dezaparvovec:

- patients had no detectable Factor IX inhibitors at baseline,
- formation of Factor IX inhibitors to Etranacogene dezaparvovec was not observed after treatment.

Patients should be monitored through appropriate clinical observations and laboratory tests for the development of Factor IX inhibitors before and after Etranacogene dezaparvovec administration (Table 3).

Table 3. Factor IX inhibitor assessment before and after administration of ETRANACOGENE DEZAPARVOVEC

Before administration of Etranacogene dezaparvovec, baseline testing of FIX inhibitors is required as follows:	After administration of Etranacogene dezaparvovec
In case of a positive test result for human Factor IX inhibitors, a re-test within approximately 2 weeks should be performed. If both the initial test and re-test results are positive, the patient should not receive Etranacogene dezaparvovec	In case increased plasma Factor IX activity levels are not achieved, decrease, or bleeding is not controlled or returns, post-dose testing for Factor IX inhibitors is recommended along with Factor IX activity testing.

3 Important information to communicate to the patient/caregiver

Ensure that you have informed the patient of the risks of Hepatotoxicity, Thromboembolic events, Malignancy as a result of vector integration, Germline and horizontal transmission of Etranacogene dezaparvovec and Development of FIX inhibitors, as described in Section 2.

Before a treatment decision is made, you should discuss the risks, benefits, and uncertainties with the patient including following: (Table 4)

Table 4. Topics for discussion with the patient or caregiver

Topics for discussion	Additional information
The potential need of **corticosteroid administration,** to manage liver damage after Etranacogene dezaparvovec treatment.	See Section 2.a
The need for: ● adequate monitoring of patients' **liver function** ● avoidance of concomitant use of **hepatotoxic medication** or agents, to minimise the risk of hepatoxicity and a potential reduced therapeutic effect of Etranacogene dezaparvovec.	See Section 2.a
The need to monitor the potential presence of **Factor IX inhibitors** after Etranacogene dezaparvovec treatment.	See Section 2.e
The possibility that **high titres of preexisting neutralising anti-AAV5 antibodies** may reduce the efficacy of Etranacogene dezaparvovec therapy.	Prior to the treatment with Etranacogene dezaparvovec, patients should be assessed for the titre of preexisting neutralising anti-AAV5 antibodies.

The possibility of **not responding to treatment** with Etranacogene dezaparvovec.	● Patients who do not respond are still exposed to long term risks. ● There will be no possibility to readminister Etranacogene dezaparvovec for patients who do not respond or have lost the response.
Long-term Etranacogene dezaparvovec effects cannot be predicted.	Patients should be reminded of the importance to enrol in a follow-up study to follow Haemophilia patients for 15 years, to substantiate the long-term safety and efficacy of Hemgenix gene therapy.
The **Patient/Caregiver guide** and **Patient Card**	**Patient/Caregiver guide** ● Make sure you provide the patient with the Patient/Caregiver guide before a decision is made about treatment with Etranacogene dezaparvovec. ● Encourage the patient to read the guide carefully, discuss it with you if there are any questions, and refer to it regularly. **Patient Card** ● Make sure you complete the Patient Card and give it to the patient on the day of administration. ● Ensure that the patient understands ○ they must always carry the Patient Card with them throughout their life ○ they must present the Patient Card to any healthcare professionals, doctors or nurses, that the patient may need to consult.

4 Adverse event notifications

Report any suspected adverse reactions to:
National Pharmacovigilance Center (NPC) - Saudi Food and Drug Authority
SFDA call center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa

CSL Behring:
Email: phvsa@cslbehring.com
Website: https://www.cslbehring.sa/en/report-adverse-event

5 Additional information

To obtain copies of the various documents, you can contact the CSL Behring Medical Information Service:

Email: MEAmedicalinfo@cslbehring.com

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