CSL Behring

This educational material is provided by CSL Behring Ltd and is mandatory as a condition of the Marketing Authorisation in order to further minimise important selected risks.

# Healthcare Professional Guide

## HEMGENIX®▼ (etranacogene dezaparvovec)

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals and patients are asked to report any suspected adverse reactions.

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

HEMGENIX® RMP Healthcare Professional Guide
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# What information can you find in this Healthcare Professional Guide?





# 1. What is HEMGENIX®?

HEMGENIX® (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 (factor IX-Padua) gene under the control of a liver-specific promoter (LP1). HEMGENIX® is produced in insect cells by recombinant DNA technology.

## a. How does HEMGENIX® work?

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

## b. Indication

HEMGENIX® 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 HEMGENIX®

### 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:

- The patient's liver health should be evaluated before administration of HEMGENIX® and closely monitored after treatment with HEMGENIX® (see Table 1)
- It is recommended that the patient's hepatic function be 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 HEMGENIX® **avoid concomitant use of hepatotoxic medication or agents,** as this may reduce the efficacy of HEMGENIX® and increase the risk for more serious hepatic reactions, particularly during the first year following HEMGENIX® administration
- Treating physicians should **ensure that patients are available for frequent monitoring of hepatic laboratory parameters after administration of HEMGENIX®**

**Table 1.** Hepatic function and factor IX activity monitoring.

| | Measurements* | Time frame | Monitoring frequency† |
|---|---|---|---|
| **Before administration** | Liver function tests | Within 3 months prior to infusion and repeated at least once prior to HEMGENIX® administration | Baseline measurement |
| | Recent fibrosis assessment | Within 6 months prior to infusion | |
| **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)<br>• 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)<br>• 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 for monitoring over time, particularly during the time frame for corticosteroid treatment decision making, to minimise the impact of inter-laboratory variability.

†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: | You should consider: |
|---|---|
| • ALT increase to above the upper limit of normal; or<br>• ALT increase to double the patient's baseline levels | • A course of corticosteroid treatment to dampen the immune response (see Table 2)<br>• Human factor IX activity measurements |

**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 5 mg/week |

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

Follow-up monitoring of transaminases in all patients who develop 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-haemophiliac population.

In patients with haemophilia B with pre-existing risk factors for thromboembolic events, such as a history of cardiovascular or cardiometabolic disease, arteriosclerosis, hypertension, diabetes, or advanced age, the potential risk of thrombogenicity may be higher. In clinical studies with HEMGENIX®, 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 HEMGENIX® 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 HEMGENIX®

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

In the event that a malignancy occurs, the treating healthcare professional should contact CSL Behring UK to obtain instructions on collecting patient samples for potential vector integration examination and integration site analysis.

**d. Potential risk of germline and horizontal transmission of HEMGENIX®**

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

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

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

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

To mitigate the potential risk for germline and 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 factor IX inhibitors**

There is no clinical experience with administration of HEMGENIX® in patients who have or had inhibitors to factor IX. It is not known whether or to what extent such pre-existing factor IX inhibitors may affect the safety or efficacy of HEMGENIX®. In patients with a history of factor IX inhibitors, HEMGENIX® treatment is not indicated.

In clinical studies with HEMGENIX®:

- Patients had no detectable factor IX inhibitors at baseline
- Formation of factor IX inhibitors to HEMGENIX® 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 HEMGENIX® administration (see Table 3).

**Table 3.** Factor IX inhibitor assessment before and after administration of HEMGENIX®.

| **Before administration of HEMGENIX®, baseline testing of factor IX inhibitors is required as follows:** | **After administration of HEMGENIX®:** |
|---|---|
| In case of a positive test result for human factor IX inhibitors, a retest within approximately 2 weeks should be performed. If both the initial test and retest results are positive, the patient should not receive HEMGENIX®. | 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 HEMGENIX®, and development of factor IX inhibitors, as described in Section 2.**

**Before a treatment decision is made**, you should discuss the risks, benefits, and uncertainties with the patient, including the topics listed in Table 4.

**Table 4.** Topics for discussion with the patient or caregiver

| Topics for discussion | Additional information |
|---|---|
| The potential need for **corticosteroid administration** to manage liver damage after HEMGENIX® treatment | See Section 2.a |
| The need for:<br>• Adequate monitoring of patients' **liver function**<br>• Avoidance of concomitant use of **hepatotoxic medication** or agents, to minimise the risk of hepatoxicity and a potential reduced therapeutic effect of HEMGENIX® | See Section 2.a |
| The need to monitor for the potential presence of **factor IX inhibitors** after HEMGENIX® treatment | See Section 2.e |
| The possibility that **high titres of pre-existing neutralising anti-AAV5 antibodies** may reduce the efficacy of HEMGENIX® therapy | Prior to treatment with HEMGENIX®, patients should be assessed for the titre of pre-existing neutralising anti-AAV5 antibodies |
| The possibility of **not responding to treatment** with HEMGENIX® | • Patients who do not respond are still exposed to long-term risks<br>• There will be no possibility to re-administer HEMGENIX® for patients who do not respond or have lost the response |
| **Long-term effects of HEMGENIX®** cannot be predicted | Patients should be reminded of the importance of enrolling in a follow-up study to follow haemophilia patients for 15 years, to substantiate the long-term safety and efficacy of HEMGENIX® gene therapy |
| **Patient/Caregiver Guide** | • Make sure you provide the patient with the Patient/Caregiver Guide before a decision is made about treatment with HEMGENIX®<br>• Encourage the patient to read the guide carefully, discuss it with you if they have 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<br>• Ensure that the patient understands:<br>- They must always carry the Patient Card with them throughout their life<br>- They must present the Patient Card to any healthcare professional that the patient may need to consult |



## 4. Adverse event notifications

Suspected Adverse drug reactions (ADRs) should be reported to the MHRA through the Yellow Card Scheme. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, call 0800 731 6789 for free, Monday to Friday between 9am and 5pm (messages can be left outside these hours). You can also report via some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank). When reporting please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

Adverse events should also be reported to CSL Behring UK Ltd on 01444 447 405.

## 5. Additional information

This guide and other documents developed as part of the HEMGENIX® risk management plan can be downloaded at www.medicines.org.uk. The eMC website is managed and owned by Datapharm Communications Limited. CSL Behring UK Ltd publishes risk management materials on this independent website.

For more information, please refer to the HEMGENIX® SmPC, which is also available at www.medicines.org.uk.

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