Package leaflet: Information for the user

Hemgenix 1 x 10^{13} genome copies/mL concentrate for solution for infusion
etranacogene dezaparvovec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Your doctor will give you a Patient Card. Read it carefully and follow the instructions on it.

What is in this leaflet

1. What Hemgenix is and what it is used for

What Hemgenix is and what it is used for

Hemgenix is a gene therapy product that contains the active substance etranacogene dezaparvovec. A gene therapy product works by delivering a gene into the body to correct a genetic defect.

Hemgenix is used for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adults who do not have current or past inhibitors (neutralising antibodies) against the Factor IX protein.

People with Haemophilia B are born with an altered form of a gene needed to make Factor IX, an essential protein required for blood to clot and stop any bleeding. People with Haemophilia B have insufficient levels of Factor IX and are prone to internal or external bleeding episodes.

How Hemgenix works

The active substance in Hemgenix is based on a virus that does not cause disease in humans. This virus has been modified so that it cannot spread in the body but can deliver a copy of the Factor IX gene into the liver cells. This allows the liver to produce the Factor IX protein and

raise the levels of working Factor IX in the blood. This helps the blood to clot more normally and prevents or reduces bleeding episodes.

2. What you need to know before you are given Hemgenix

You must not be given Hemgenix

- If you are allergic to etranacogene dezaparvovec or to any of the other ingredients of this medicine (listed in section 6).

- If you suffer from an active infection which is either an acute (short-term) infection, or chronic (long-term) infection that is not controlled by medicines.

- If your liver does not work properly due to advanced liver fibrosis (tissue scarring and thickening), or cirrhosis (scarring due to long-term liver damage).

If any of the above applies to you, or if you are unsure of any of the above, please talk to your doctor before you receive Hemgenix.

Warnings and precautions

Before the treatment with Hemgenix

Your doctor will perform several tests **before** you are given Hemgenix treatment.

Antibody blood tests
Your doctor will conduct blood tests to check for certain antibodies (proteins) before treatment with Hemgenix, including:

- Blood tests to check for the presence of antibodies in your blood directed against the human Factor IX protein (Factor IX inhibitors).
  If you test positive for these antibodies, another test will be performed in approximately 2 weeks. If both the initial test and re-test results are positive, Hemgenix administration will not be initiated.

- Blood tests to check for the amount of antibodies in your blood directed against the type of virus used to make Hemgenix may also be performed.

Liver health
In order to decide if this medicine is suitable for you, your doctor will check the status of your liver health before you start treatment with Hemgenix and perform:

- Blood tests to check the level of liver enzyme in your blood
- Liver ultrasound
- Elastography testing to check for scarring or thickening of your liver.

During or shortly after Hemgenix infusion

Your doctor will monitor you **during or shortly after** Hemgenix infusion.

Infusion-related reactions

Infusion-related side effects can occur during or shortly after you are given the Hemgenix infusion (drip). Your doctor will monitor you during Hemgenix infusion and for at least 3 hours after you are given Hemgenix.

- Symptoms of such side effects are listed in section 4 "Possible side effects". Tell your doctor or nurse **immediately** if you experience these or any other symptoms during or shortly after the infusion.

- Depending on your symptoms, your infusion may be slowed down or interrupted. If the infusion is interrupted, it can be restarted at a slower rate when the infusion reaction is resolved. Your doctor may also consider if you should be given corticosteroids (e.g. prednisolone or prednisone) to help manage the infusion reaction.

<u>After the treatment with Hemgenix</u>

After treatment with Hemgenix, your doctor will continue to check your health. It is **important** that you **discuss the schedule for these blood** tests with your doctor so that they can be carried out as necessary.

<u>Liver enzymes</u>
Hemgenix will trigger a response within your immune system that could lead to an increased level of certain liver enzymes in your blood called transaminases (transaminitis). Your doctor will regularly monitor your liver enzyme levels to ensure that the medicine is working as it should:

- In the first 3 months, at least, after you are given Hemgenix, you will have blood tests once per week to monitor your liver enzyme levels.
    - If you experience an increase in liver enzymes, you may have more frequent blood tests to check the levels of your liver enzymes, until they return to normal. You may also need to take another medicine (corticosteroids) to manage these side effects.
    - Your doctor may also perform additional tests to exclude other causes for the increase in your liver enzymes, if needed, in consultation with a doctor experienced in liver diseases.

- Your doctor will repeat liver enzyme testing tests every three months from month 4 up to one year after you are given Hemgenix to continue checking of your liver health. In the second year after you are given Hemgenix, your doctor will follow up your liver enzymes half-yearly. After the second year, your doctor will check your liver enzymes annually for at least 5 years after you are given Hemgenix.

<u>Factor IX levels</u>
Your doctor will regularly check your Factor IX levels to see if treatment with Hemgenix was successful.

- In at least the first 3 months after you are given Hemgenix, you will have blood tests once per week to check your Factor IX levels.

- Your doctor will repeat these tests every three months from month 4 up to 1 year after you are given Hemgenix to continue checking your Factor IX level. In the second year after you are given Hemgenix, your doctor will check your Factor IX levels half-yearly. Thereafter, your doctor will check them annually at least for 5 years after you are given Hemgenix.

- If you experience an increase in liver enzymes or will need to take another medicine (e.g. corticosteroids), you will have more frequent blood tests to check your Factor IX levels, until your liver enzymes return to normal or you stop taking your additional medicine.

Use of other Haemophilia treatments

After Hemgenix use, talk to your doctor about if or when you should stop your other Haemophilia treatments and develop a treatment plan of what to do in case of surgery, trauma, bleeds, or any procedures that could potentially increase the risk of bleeding. It is very important to continue your monitoring and doctor visits to determine if you need to take other treatments to manage Haemophilia.

Abnormal clotting of blood (thromboembolic events)

After treatment with Hemgenix, your Factor IX protein level may increase. In some patients, it could increase to levels above the normal range for a period of time.

- Unusually elevated Factor IX levels may cause your blood to clot abnormally, increasing the risk of blood clots, such as in the lung (pulmonary thromboembolism) or in a blood vessel of the leg (venous or arterial thrombosis). This theoretical risk is low due to your inborn deficiency in the clotting cascade when compared with healthy subjects.

- You may be at risk of abnormal blood clotting, if you have preexisting problems with your heart and blood vessels (e.g. a history of a heart disease (cardiovascular disease), thick and stiff arteries (arteriosclerosis), high blood pressure (hypertension), or if you are diabetic or above 50 years.

- Your doctor will regularly monitor your blood for any potential abnormalities in Factor IX levels, in particular if you continue receiving your routine Factor IX prophylaxis (Factor IX replacement therapy) after Hemgenix administration (see also section 3 “How to use Hemgenix”).

- Consult your doctor immediately, if you observe signs of abnormal clotting, such as sudden chest pain, shortness of breath, sudden onset of muscle weakness, loss of sensation and/or balance, decreased alertness, difficulty in speaking, or swelling of one or both legs.

Avoiding blood donations and donations for transplantations

The active substance in Hemgenix may temporarily be excreted through your blood, semen, breast milk or bodily waste, a process called shedding (see also section 2 “Pregnancy, breast-feeding and fertility”).

To ensure that people without Haemophilia B are not exposed to Hemgenix DNA through shedding process in your body and/or semen, you will not be able to donate blood, semen, or organs, tissues and cells for transplantation after you have been treated with Hemgenix.

Immunocompromised patients or patients with HIV or other infection

If you have problems with your immune system (are immunocompromised), are undergoing or will undergo a treatment suppressing your immune system or have an HIV or other new or recent infection, your doctor will decide where you will be able to receive Hemgenix.

Neutralising antibodies against Factor IX proteins (Factor IX inhibitors)

Neutralising antibodies against Factor IX proteins may stop Hemgenix from working properly. Your doctor may check your blood for these antibodies, if your bleeds will not be controlled, or return after you have been given Hemgenix (see also section 3 “How to use Hemgenix”).

Receiving gene therapy again in the future

After receiving Hemgenix, your immune system will produce antibodies to the shell of the AAV vector. It is not yet known whether or under which conditions therapy with Hemgenix may be repeated. It is also not yet known whether or under which conditions subsequent use of another gene therapy may be possible.

Risk of malignancy potentially associated with Hemgenix

- Hemgenix will insert into liver cells and it could possibly insert into the liver cell DNA or the DNA of other body cells. As a consequence, Hemgenix could contribute to a risk of cancer, such as liver cancer (hepatocellular carcinoma). Although there is no evidence of this in the clinical studies so far, this remains possible because of the nature of the medicine. You should therefore discuss this with your physician.

- If you are a patient with preexisting risk factors for hepatocellular carcinoma (e.g. you have liver fibrosis (scarring and thickening of the liver), or Hepatitis B, Hepatitis C, fatty liver (nonalcoholic fatty liver disease (NAFLD)), or you excessively drink alcohol), your doctor will regularly (e.g. annually) monitor your long-term liver health for at least 5 years after Hemgenix administration and perform the following tests:
  - Annual liver ultrasound and
  - Annual blood test to check for increases in so-called alpha-fetoprotein.

- After treatment with Hemgenix, you will be expected to enrol in a follow up study to help study the long-term safety of the treatment for 15 years, how well it continues to work and any side effects that may be linked to the treatment. In the event of cancer, your doctor may take a sample of your cancer (biopsy) to check if Hemgenix has inserted into the cell DNA.

Children and adolescents

Hemgenix has not been studied in children or adolescents under the age of 18.

Other medicines and Hemgenix

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

If you are taking medication that are known to damage the liver (hepatotoxic medication), your doctor may decide that you may need to stop this medication to be able to receive Hemgenix.

Pregnancy, breast-feeding and fertility

There are no data regarding Hemgenix use in women with Haemophilia B.

If you are pregnant or breast-feeding, think you may be pregnant or plan to become pregnant, ask your doctor for advice prior to be given Hemgenix.

- Hemgenix treatment is not recommended in women who are able to become pregnant. It is not yet known whether Hemgenix can be used safely in these patients as the effects on pregnancy and the unborn child are not known.

- Hemgenix should not be used during pregnancy. It is not known whether this medicinal product can cause harm to your unborn baby when administered to you during your pregnancy.

- Hemgenix should not be used during breast-feeding. It is unknown whether this medicine is excreted in human milk. A risk to the newborns/infants cannot be excluded.

Use of contraception and avoiding partner pregnancy for a period of time

After a male patient has been treated with Hemgenix, the patient and any female partner must avoid pregnancy for 12 months. You should use effective contraception (e.g. barrier contraception such as condom or diaphragm). This is to prevent the theoretical risk that the Factor IX gene from a father's Hemgenix treatment is transmitted to a child with unknown consequences. For the same reason, male patients must not donate semen. Discuss with your doctor which methods of contraception are suitable.

Driving and using machines

Hemgenix has minor influence on the ability to drive and use machines. Temporary dizziness, tiredness, and headaches have occurred shortly after Hemgenix infusion. If you are affected, you should use caution until you are certain that Hemgenix does not adversely affect your ability to drive or use machines. Talk to your doctor about this.

Hemgenix contains sodium and potassium

- The medicine contains 35.2 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.8% of the recommended maximum daily dietary intake of sodium for an adult.

- This medicinal product contains potassium, less than 1 mmol (39 mg) per vial, that is to say essentially potassium-free.

3. How Hemgenix is given

Hemgenix will be given to you in a hospital setting under direction of a doctor experienced and trained in the treatment of your condition Haemophilia B.

Hemgenix will be given to you **only once** by a single slow infusion (drip) into a vein. The infusion will take usually 1 to 2 hours to be completed.

Your doctor will work out the correct dose for you, based on your body weight.

Discontinuation of exogenous Factor IX treatment

- It may take several weeks before improved bleeding control becomes apparent after Hemgenix infusion, and you may need to continue your replacement therapy with exogenous Factor IX during the first weeks after Hemgenix infusion.

- Your doctor will regularly monitor your blood for the Factor IX activity levels, i.e. weekly for at least first 3 months, and at regular intervals thereafter, and decide if and when you should receive, reduce, or stop your exogenous Factor IX therapy (see section 2).

If you have any questions on the use of Hemgenix ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects were observed in clinical studies with Hemgenix.

Very Common (may occur with more than 1 in 10 patients)
- Headache
- Increased levels of liver enzymes in the blood (Alanine aminotransferase increased)
- Increased levels of liver enzymes in the blood (Aspartate aminotransferase increased)
- Flu-like illness (Influenza-like illness)
- Increased levels of C-reactive protein, a marker of inflammation
- Infusion related reaction (allergic reactions (hypersensitivity), infusion site reaction, dizziness, eye itching (pruritus), reddening of the skin (flushing), upper tummy (abdominal) pain, itchy rash (urticaria), chest discomfort, and fever)

Common (may occur with up to 1 in 10 patients)
- Dizziness
- Feeling sick (Nausea)
- Tiredness (Fatigue)
- Feeling generally unwell (Malaise)
- Increased blood levels of bilirubin, a yellow breakdown substance of the red blood cells
- Increased blood levels of creatine phosphokinase, an enzyme (protein) found mainly in the heart, brain and skeletal muscle

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly – please see details below.

UK: Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store	Ireland: HPRA Pharmacovigilance Earlsfort Terrace IRL - Dublin 2 Tel: +353 1 6764971 Fax: +353 1 6762517 Website: www.hpra.ie Email: medsafety@hpra.ie

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Hemgenix

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP.

Store in a refrigerator (2 °C - 8 °C). Do not freeze.
Store vials in the original package in order to protect from light.

Dilute before use.
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, Hemgenix can be stored at 15 °C - 25 °C in the infusion bag protected from light for up to 24 hours after the dose preparation.

Do not use this medicine if you notice particles, cloudiness or discolouration.

6. Contents of the pack and other information

What Hemgenix contains

- The active substance is etranacogene dezaparvovec. Each mL of etranacogene dezaparvovec contains 1 x 10^{13} gene copies (gc)/mL.

- The other ingredients (excipients) are sucrose, polysorbate-20, potassium chloride, potassium dihydrogen phosphate, sodium chloride, sodium hydrogen phosphate, hydrochloric acid (for pH adjustment), water for injections (see also section 2 “Hemgenix contains sodium and potassium.”).

This medicine contains genetically modified organisms.

What Hemgenix looks like and contents of the pack

Hemgenix is a concentrate for solution for infusion (sterile concentrate).

Hemgenix is a clear, colourless solution.

Hemgenix is supplied in a vial containing 10 mL of etranacogene dezaparvovec.

The total number of vials in a pack, corresponds to the dosing requirement for an individual patient depending on his body weight, and is provided on the package.

Marketing Authorisation Holder and Manufacturer
CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

United Kingdom (Great Britain)
CSL Behring UK Ltd.
Tel: +44 1444 447405

Ireland and United Kingdom (Northern Ireland)
CSL Behring GmbH
Tel: +49 69 305 17254

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This medicine has been given 'conditional approval'.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics (SmPC) before using.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified organisms (GMOs).

Personal protective equipment, including gloves, safety goggles, protective clothing and masks, should be worn while preparing and administering etranacogene dezaparvovec.

Preparation of etranacogene dezaparvovec prior to administration

1. Use aseptic techniques during the preparation and administration of etranacogene dezaparvovec.
2. Use etranacogene dezaparvovec vial(s) only once (single-use vial(s)).
3. Verify the required dose of etranacogene dezaparvovec based on the patient's body weight. The total number of vials in each finished pack corresponds to the dosing requirement for each individual patient based on the body weight.
4. Etranacogene dezaparvovec must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration.
    - Withdraw the volume of the calculated Hemgenix dose (in mL) from the 500 mL-infusion bag(s) with sodium chloride 9 mg/mL (0.9%) solution for injection. The volume to be withdrawn will vary based on the patient body weight.

- For patients <120 kg body weight, withdraw the volume of sodium chloride 9 mg/mL (0.9%) solution for injection corresponding to the total Hemgenix dose (in mL) from one 500 mL-infusion bag.
- For patients ≥120 kg body weight, withdrawn the volume of sodium chloride 9 mg/mL (0.9%) solution for injection corresponding to the total Hemgenix dose (in mL) from two 500 mL-infusion bags, by withdrawing half of the volume from each of the two 500 mL-infusion bags.

- Add subsequently the required Hemgenix dose to the infusion bag(s) to bring the total volume in each infusion bag back to 500 mL.

5. Add the Hemgenix dose directly into the sodium chloride 9 mg/mL (0.9%) solution for injection. Do not add the Hemgenix dose into the air within the infusion bag during diluting.
6. Gently invert the infusion bag(s) at least 3 times to mix the solution and ensure even distribution of the diluted product.
7. To avoid foaming:

- Do not shake the etranacogene dezaparvovec vial(s) and the prepared infusion bag(s).
- Do not use filter needles during preparation of etranacogene dezaparvovec.

8. To reduce the risk of spillage and/or aerosol formation, the infusion bag(s) should be provided connected to an infusion tubing prefilled with sterile sodium chloride 9 mg/mL (0.9%) solution for injection.
9. The infusion tubing prefilled with sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be connected to the main intravenous infusion line also primed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection prior to use.
10. Use only sodium chloride 9 mg/mL (0.9%) solution for injection since the stability of etranacogene dezaparvovec has not been determined with other solutions and diluents.
11. Do not infuse the diluted etranacogene dezaparvovec solution in the same intravenous line with any other products.
12. Do not use a central line or port.

Administration

13. Diluted etranacogene dezaparvovec should be visually inspected prior to administration. The diluted etranacogene dezaparvovec should be a clear, colourless solution. If particulates, cloudiness or discoloration are visible in the infusion bag, do not use etranacogene dezaparvovec.
14. Use the product after dilution as soon as possible. You must not exceed the storage time of the diluted product beyond that provided in SmPC section 6.3.
15. Use an integrated (in-line) 0.2 µm filter made out of polyethersulfone (PES).
16. The diluted etranacogene dezaparvovec solution must be administered into a peripheral vein by a separate intravenous infusion line through a peripheral venous catheter.
17. Etranacogene dezaparvovec solution should be infused closely following the infusion rate(s) provided in SmPC section 4.2. The administration should be completed within ≤24 hours after the dose preparation (see SmPC section 4.2).
18. After the entire content of the infusion bag(s) is infused, the infusion line must be flushed at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure all etranacogene dezaparvovec is delivered.

Measures to take in case of accidental exposure

In case of accidental exposure local guidance for pharmaceutical waste must be followed.

- In case of accidental exposure to eyes, immediately flush eyes with water for at least 15 minutes. Do not use alcohol solution.

- In case of accidental needle stick exposure, encourage bleeding of the wound and wash injection area well with soap and water.
- In case of accidental exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. Do not use alcohol solution.
- In case of accidental inhalation, move the person into fresh air.
- In case of accidental oral exposure, abundantly rinse mouth with water.
- In each case, obtain subsequently medical attention.

Work surfaces and materials which have potentially been in contact with etranacogene dezaparvovec must be decontaminated with appropriate disinfectant with viricidal activity (e.g. a chlorine releasing disinfectant like hypochlorite containing 0.1% available chlorine (1000 ppm)) after usage.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and disposable material that may have come in contact with Hemgenix (solid and liquid waste) must be disposed of in compliance with the local guidance for pharmaceutical waste. The risk of an adverse effect to human health upon accidental exposure to Hemgenix and the environmental risks are, however, considered negligible.
Caregivers should be advised on the proper handling of waste material generated from contaminated medicinal ancillaries during Hemgenix use.

Work surfaces and materials which have potentially been in contact with etranacogene dezaparvovec must be decontaminated with appropriate disinfectant with viricidal activity (e.g. a chlorine releasing disinfectant like hypochlorite containing 0.1% available chlorine (1000 ppm)) after usage and then autoclaved, if possible.