▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

HEMGENIX®

(Etranacogene dezaparvovec) – Injection for intravenous infusion

1 NAME OF THE MEDICINE

Etranacogene dezaparvovec

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

HEMGENIX® is a gene therapy medicinal product that employs a non-replicating adeno-associated viral vector serotype 5 (AAV5) containing a codon-optimised coding DNA sequence for the human coagulation factor IX variant R338L (FIX-Padua) under the control of a liver-specific promoter (LP1). Etranacogene dezaparvovec is produced using recombinant baculovirus technology.

Each 1 mL of HEMGENIX® contains 1 x 10^{13} genome copies (gc).

Each vial contains an extractable volume of not less than 10 mL of injection for intravenous infusion, containing a total of 1 x 10^{14} genome copies.

The total number of vials in each finished pack is customised to meet dosing requirements for the individual patient, based on their body weight (see section 4.2 Dose and method of administration and 6.5 Nature and contents of container).

The medicinal product contains 35.2 mg sodium per vial (3.52 mg/mL). For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Injection for intravenous infusion.

HEMGENIX® is a clear colourless solution.

After dilution, HEMGENIX® should be a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

This medicine has **provisional approval** in Australia.

HEMGENIX® is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with haemophilia B (congenital factor IX deficiency), without a history of factor IX inhibitors, who:

- currently use factor IX prophylaxis therapy, or
- have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes.

The decision to approve this indication has been made on the basis of short-term efficacy and safety data from the clinical trial program. Continued approval of this indication depends on confirmation of longer-term benefit from ongoing clinical trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

For single-dose intravenous infusion only.

HEMGENIX® can be administered only once. After infusion with HEMGENIX®, an immune response to the AAV5 capsid proteins will occur, therefore the patient should not be re-dosed.

HEMGENIX® must be prescribed and administered in a clinical treatment centre under the supervision of a haematologist or physician with experience in the diagnosis and management of haemophilia B**.** HEMGENIX® should be administered in a setting where personnel and equipment are immediately available to treat infusion related reactions.

Patient assessment

For patient assessment, baseline testing is required. This includes examinations of:

- Pre-existing neutralising anti-AAV5 antibody titre (see section 4.4, sub-section Immune-mediated neutralisation of the AAV5 vector capsid and section 5.1 Pharmacodynamic properties – Clinical trials). An assay for neutralising anti-AAV5 antibodies should be used.
- Factor IX inhibitor presence.

  In case of a positive test result for human factor IX inhibitors, a re-test should be performed. If the patient is confirmed as having factor IX inhibitors, they should not receive HEMGENIX®.

- Liver health, including:
  - Enzyme testing (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin). It is recommended that the ALT test is repeated at least once prior to HEMGENIX® administration to establish patient's ALT baseline.
  - Hepatic ultrasound and elastography.

  In case of radiological liver abnormalities and/or sustained liver enzyme elevations, consideration of a consultation with a hepatologist is recommended to assess eligibility for HEMGENIX® (see section 4.4, sub-section Hepatotoxicity).

  If there are signs or symptoms of acute or uncontrolled chronic active infections, HEMGENIX® treatment must be postponed until the infection has resolved or is controlled (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use, sub-section Patients with active or uncontrolled chronic infections).

Dosage

The recommended dose of HEMGENIX® is a single dose of 2×10^{13} gc per kilogram (kg) of body weight, corresponding to 2.0 mL/kg body weight. This is administered as an intravenous infusion after dilution with 0.9% sodium chloride solution (normal saline) (see sub-section Preparation of HEMGENIX® for administration and section 6.6 Special precautions for disposal).

The dose should be calculated as follows:

HEMGENIX® dose (in mL) = **patient body weight** (in kilogram) x **2**

Patients should be carefully assessed prior to receiving HEMGENIX® and monitored closely afterwards. Refer to section 4.2 Dose and method of administration, sub-section Patient assessment for details of the required tests and assessments to be carried out before treatment and see section 4.4 Special warnings and precautions for use; sub-section Laboratory testing and monitoring for details of required monitoring to be carried out following treatment.

Method of administration

General instructions for a genetically modified organism

HEMGENIX® contains a genetically modified organism (GMO), see section 6.6 Special precautions for disposal for further information. Follow local institutional biosafety guidelines for the handling and disposal of medicinal products containing a GMO.

Personal protective equipment, including gloves, safety goggles, protective clothing and masks, should be worn while preparing, handling or administering HEMGENIX®. Personnel should not work with HEMGENIX® if skin is cut or scratched.

Accidental exposure to HEMGENIX® should be avoided. Local guidelines on handling of materials that have been in contact with the GMO should be followed in case of accidental exposure. Work surfaces and materials which have potentially been in contact with HEMGENIX® must be decontaminated with appropriate disinfectant.

- 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 medical attention.

Due to the non-replicating nature of the shed vector DNA fragments, the risk of an adverse effect to human health upon accidental exposure and the environmental risks are considered negligible.

Preparation of HEMGENIX® for administration

HEMGENIX® is for single use in one patient only. Discard any residue as described in section 6.6 Special precautions for disposal.

HEMGENIX® is administered as a single intravenous infusion after dilution of the required dose with 0.9% normal saline.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

1. HEMGENIX® does not contain preservatives. Use aseptic techniques during the preparation and administration of HEMGENIX®.
2. Use HEMGENIX® vial(s) only once (single-use vial(s)).
3. Verify the required dose of HEMGENIX® based on the patient's body weight. The total number of vials in each finished pack is prepared for the dosing requirement for each individual patient based on the body weight.

The individual patient dose may not require the full volume provided in the finished pack. Any un-used volume of HEMGENIX® exceeding the required dose must be discarded (see section 6.6 Special precautions for disposal).

4. To avoid foaming:
   - ► **Do not** shake the HEMGENIX® vial(s) or the prepared infusion bag(s).
   - ► **Do not** use filter needles during preparation of HEMGENIX®.
5. HEMGENIX® must be diluted with 0.9% normal saline solution prior to administration.
   - ► Prior to dilution, withdraw the volume of the calculated HEMGENIX® dose (in mL) from the 500 mL infusion bag(s) with 0.9% normal saline solution (see section 6.3 Shelf life). The volume of 0.9% normal saline to be removed from the infusion bag(s) will vary based on the patient body weight.
     - o For patients < 120 kg body weight, dilute HEMGENIX® in one 500 mL-0.9% normal saline solution infusion bag.
     - o For patients ≥ 120 kg body weight, dilute HEMGENIX® with two 500 mL-0.9% normal saline solution infusion bags by dividing the total dose of HEMGENIX® equally between two 500 mL infusion bags.
   - ► Remove the amount of 0.9% normal saline with a luer lock syringe at the mixing adapter site of the applicable connector.
   - ► Add the volume of the required HEMGENIX® dose to the infusion bag(s) to bring the total volume in each infusion bag back to 500 mL.
6. **Do not** add HEMGENIX® into the airspace of the infusion bag during diluting.
7. Gently invert the infusion bag(s) at least 3 times to mix the solution and ensure even distribution of the diluted product.
8. To reduce the risk of spillage and/or aerosol formation, the infusion bag(s) should be connected to an infusion tubing prefilled with sterile 0.9% normal saline solution.
9. The infusion tubing prefilled with sterile 0.9% normal saline solution should be connected to the main intravenous infusion line which has been primed with sterile 0.9% normal saline solution prior to use.
10. Use only 0.9% normal saline solution since the stability of HEMGENIX® has not been determined with other solutions and diluents.
11. **Do not** infuse the diluted HEMGENIX® solution in the same intravenous line with any other products.
12. **Do not** use a central line or port.

Administration of HEMGENIX®

13. Diluted HEMGENIX® should be visually inspected prior to administration. The diluted HEMGENIX® should be a clear, colourless solution. If particulates, cloudiness or discoloration are visible in the infusion bag, do not use HEMGENIX®.
14. Use the product as soon as possible after dilution. You **must not** exceed the 6 hours storage time of the diluted product (see section 6.3 Shelf life).
15. Use an integrated (in-line) 0.2 µm filter made out of polyethersulfone (PES) (see section 6.2 Incompatibilities).
16. The diluted HEMGENIX® solution must be administered into a peripheral vein by a separate intravenous infusion line through a peripheral venous catheter.
17. The diluted HEMGENIX® solution should be administered at a constant infusion rate of 500 mL/hour (8 mL/min).

    HEMGENIX® **must not** be administered as an intravenous push or bolus.

    In the event of an infusion reaction during administration, the infusion rate should be slowed or stopped to ensure patient tolerability (see section 4.4 Special warnings and precautions for use). If the infusion is stopped, it may be restarted at a slower rate when the infusion reaction is resolved.

    If the infusion rate needs to be reduced, or stopped and restarted, the HEMGENIX® solution should be infused within the shelf life of the diluted HEMGENIX® solution, i.e. within 6 hours after the dose preparation (see section 6.3 Shelf life).
18. After the entire content of the infusion bag(s) is infused, the infusion line must be flushed at the same infusion rate with 0.9% normal saline solution to ensure all HEMGENIX® is delivered.

The healthcare professional should provide the patient card to the patient after administration with HEMGENIX® and provide instructions on how to use the card.

For information on managing factor IX levels as HEMGENIX® takes effect, see section 4.4 Special warnings and precautions for use, sub-section Discontinuation of continuous routine prophylaxis with exogenous human factor IX.

Special populations

Pre-existing neutralising AAV5 antibodies

No dose adjustments are recommended for patients with pre-existing neutralising anti-AAV antibodies (see section 4.4 Special warnings and precautions, sub-section Immune-mediated neutralisation of the AAV5 vector capsid).

Renal impairment

No dose adjustments are recommended in patients with any level of renal impairment.

The safety and efficacy of HEMGENIX® in patients with severe renal impairment and end-stage renal disease have not been studied (see section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dose adjustments are recommended in patients with hepatic disorders (see section 5.2 Pharmacokinetic properties).

The safety and efficacy of HEMGENIX® in patients with severe hepatic impairment have not been studied. This medicinal product is not recommended for use in patients with significant hepatic disorders (see sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Paediatric population

The safety and efficacy of HEMGENIX® in children aged 0 to 18 years have not been studied. No data are available.

Elderly population

No dose adjustments are recommended in elderly patients. Limited data are available in patients over 65 years (see section 5.1 Pharmacodynamic properties, sub-section Clinical trials).

Patients with HIV

No dose adjustments are recommended in HIV-positive patients. Limited data are available in patients with controlled HIV infection (see section 4.4 Special warnings and precautions).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of excipients.

Active infections, either acute or uncontrolled chronic.

Patients with known advanced hepatic fibrosis, or cirrhosis (see section 4.4 Special warnings and precautions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Laboratory testing and monitoring

Prior to treatment, baseline tests and assessments are required. Refer to section 4.2 Dose and method of administration, sub-section Patient assessment.

Monitoring post-administration

After administration of HEMGENIX®, regular monitoring is required. This includes examinations of:

- Liver enzymes to monitor for liver enzyme elevations which may indicate immune-mediated liver hepatotoxicity (see section 4.4, sub-section Hepatotoxicity). Monitor ALT levels by testing weekly for at least 3 months following administration of HEMGENIX®. After 3 months, it is recommended to test ALT every 3 months in the first year post-treatment and every 6 months in the second year post-treatment, with subsequent yearly testing for at least 5 years to routinely assess liver function.
- Factor IX activity (e.g. weekly for at least 3 months, then every 3 months in the first year and every 6 months in the second year, with subsequent yearly testing for at least 5 years) (see section 4.4, sub-sections Hepatotoxicity, Discontinuation of continuous routine prophylaxis with exogenous human factor IX and Immune-mediated neutralisation of the AAV5 vector capsid).
    - Monitor patients regularly for their factor IX activity in particular when exogenous factor IX is administered.
    - The use of different assays and reagents may have an impact on the test results; therefore, the same assay and reagents should be used to monitor patients over time. Chromogenic substrate assays (CSA) return lower factor IX activity results compared to one-stage clotting assays (OSA). In clinical studies, the post-dose factor IX activity measured with CSA returned lower values with the mean CSA to OSA factor IX activity ratio ranging from 0.408 to 0.547.
    - Use of exogenous factor IX concentrates before and after HEMGENIX® administration may impede assessment of endogenous, etranacogene dezaparvovec-derived factor IX activity.
- For patients with pre-existing risk factors for hepatocellular carcinoma (see section 4.4 sub-heading Hepatocellular carcinogenicity), perform regular alpha-fetoprotein (AFP) level testing and abdominal ultrasound (e.g. annually) for 5 years following administration.

- Monitor patients for human factor IX inhibitors. Post-dose testing should be performed if plasma factor IX activity levels are not achieved, decrease or if bleeding is not controlled or returns.

Infusion reactions

Infusion reactions, including hypersensitivity reactions, are possible (see section 4.8 Adverse effects (Undesirable effects)). Patients should be closely monitored for infusion reactions throughout the infusion period and for at least 3 hours after end of infusion.

The recommended infusion rate provided in section 4.2 Dose and method of administration should be closely adhered to ensure patient tolerability.

In the event of an infusion reaction during administration, the infusion may be slowed or interrupted. Based on clinical judgement, treatment with e.g. a corticosteroid or antihistamine may be considered for management of an infusion reaction.

Hepatotoxicity

An immune response to the liver-directed AAV5 capsid proteins will occur after HEMGENIX® administration. Intravenous administration of a liver-directed AAV5 vector may potentially lead to elevations in liver transaminases (transaminitis). Transaminitis, particularly when observed in the first 3 months after HEMGENIX® administration, is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of the AAV-vector based gene therapy.

In clinical studies with HEMGENIX®, transient, asymptomatic and predominantly mild elevations in liver transaminases were observed, most often in the first 3 months after HEMGENIX® administration. These transaminase elevations resolved either spontaneously or with administration of a corticosteroid taper to normal levels after a period of up to several weeks (see section 4.8 Adverse effects (Undesirable effects)).

To mitigate the risk of potential hepatotoxicity, transaminases should be closely monitored, e.g. once per week for at least 3 months after HEMGENIX® administration. A course of corticosteroid taper should be considered in the event of ALT increase to above the upper limit of normal or to double the patient's baseline levels, along with human factor IX activity examinations.

The corticosteroid treatment should be started with oral 60 mg/day prednisolone or prednisone (see **Table 1**). Corticosteroid tapering should be commenced, once the ALT levels are below the upper limit of normal levels.

Table 1: Recommended prednisolone treatment applied in clinical studies with HEMGENIX®

Timeline	[1]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 baseline level has been reached	Reduce daily dose by 5 mg/week

[1]Medications equivalent to prednisolone may also be used. A combined immunosuppressant regimen or the use of other products can also be considered in case of prednisolone treatment failure or contraindication.

To assist in the interpretation of test results in case of ALT increase, monitoring of ALT may be accompanied by monitoring of AST and creatine phosphokinase (CPK) to help rule out alternative causes of ALT elevations, including potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise. Retesting of ALT levels within 24 to 48 hours should be also considered.

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.

The safety of HEMGENIX® in patients with severe hepatic impairment, including cirrhosis, severe liver fibrosis has not been studied (see sections 4.3 Contraindications and 5.2 Pharmacokinetic properties).

Discontinuation of continuous routine prophylaxis with exogenous human factor IX

It may take several weeks before improved haemostatic control becomes apparent after HEMGENIX® infusion (see section 5.1 Pharmacodynamic properties – Clinical trials and section 5.2 Pharmacokinetic properties). Therefore, continued haemostatic support with exogenous human factor IX may be required during the first weeks after HEMGENIX® administration to provide sufficient factor IX coverage for the initial days post-treatment. Monitoring of the factor IX activity is recommended post-dose to follow the patient`s response to HEMGENIX® (see sub-heading Laboratory testing and monitoring regarding consistency of factor IX tests, including differing factor IX activity results between CSA and OSA tests, and testing for factor IX inhibitors).

Routine prophylaxis with exogenous human factor IX was discontinued during the clinical studies when a subject’s endogenous factor IX activity was ≥ 5%.

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 (see section 4.1 Therapeutic indications).

In the clinical studies with HEMGENIX®, patients had no detectable factor IX inhibitors at baseline, and formation of inhibitors was not observed after treatment.

Patients should be monitored through appropriate clinical observations and laboratory tests for the development of inhibitors to factor IX after HEMGENIX® administration.

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 the clinical studies with HEMGENIX®, treatment-related thromboembolic events were not reported. In addition, no supraphysiological factor IX activity levels were observed.

Immune-mediated neutralisation of the AAV5 vector capsid

In AAV-vector based gene therapies, pre-existing neutralising anti-AAV antibodies may impede transgene expression at desired therapeutic levels.

In the clinical studies with HEMGENIX®, the subject sub-group with detectable pre-existing neutralising anti-AAV5 antibodies up to titres of 1:678 based on a clinical trial assay (equivalent to 1:898 titre based on the scientifically validated neutralising AAV5 antibody assay with an extended measure range) showed mean factor IX activity that was numerically lower compared to the subject sub-group without detectable pre-existing neutralising anti-AAV5 antibodies. However, both subject groups, with and without detectable pre-existing neutralising anti-AAV5 antibodies, demonstrated an improved haemostatic protection compared to the standard of care factor IX prophylaxis (see section 5.1 Pharmacodynamic properties – Clinical trials).

It is recommended that patients are assessed for the titre of pre-existing neutralising anti-AAV5 antibodies before treatment with HEMGENIX®. The safety and efficacy of HEMGENIX® in patients with pre-existing neutralising anti-AAV5 antibody titres above 1:678 based on a clinical trial assay (equivalent to 1:898 titre based on the scientifically

validated neutralising AAV5 antibody assay with an extended measure range) has not been established. In 1 subject with a pre-existing neutralising anti-AAV5 antibody titre of 1:3212, (using the clinical trial assay) no factor IX expression was observed and recommencement of exogenous factor IX prophylaxis was needed (see section 5.1 Pharmacodynamic properties – Clinical trials).

Hepatocellular carcinogenicity

HEMGENIX® is composed of a non-replicating AAV5 vector whose DNA was demonstrated to maintain largely in episomal form with only a few random human DNA integration events recorded. Although rare, vector integration into human genome may potentially result in insertional mutagenesis that can conceivably contribute to the development of malignancy.

In the clinical studies, no malignancies were identified in relation to treatment with HEMGENIX® (see section 5.1 Pharmacodynamic properties – Clinical trials and section 5.3 Preclinical safety data). In the event that a malignancy occurs, the treating healthcare professional should contact the sponsor to obtain instructions on collecting patient samples for potential vector integration examination and integration site analysis.

No HEMGENIX®-associated clonal expansion or carcinogenicity was observed in preclinical or clinical studies (see section 5.3 Preclinical safety data and section 5.1 Pharmacodynamic properties – Clinical trials).

One subject with pre-existing risk factors for developing hepatic cancer developed a hepatocellular carcinoma one year post-dose. The hepatocellular carcinoma was assessed as not related to HEMGENIX® treatment based on vector integration site analyses and whole genome sequencing in liver biopsies/samples.

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

Shedding

Temporary shedding of HEMGENIX® vector DNA will occur in blood, faeces and semen of patients receiving HEMGENIX® (see section 5.2 Pharmacokinetic properties). In case of accidental exposure, see section 4.2 Dose and method of administration, sub-heading General instructions for genetically modified organisms.

Male patients should be informed on the need for contraceptive measures for them and their female partners of childbearing potential. (see section 4.6 Fertility, pregnancy and lactation).

Blood, organ, tissue and cell donation

Patients treated with HEMGENIX® should not donate blood, or organs, tissues and cells for transplantation to minimise the risk of exposure to non-target individuals. This information is included in the patient card (see section 4.2 Dose and method of administration).

Caregivers should be advised on the proper handling of waste material generated from contaminated medicinal ancillaries during HEMGENIX® use (see section 6.6 Special precautions for disposal).

Immunocompromised patients

No immunocompromised patients, including patients undergoing immunosuppressive treatment within 30 days before HEMGENIX® infusion, were enrolled in clinical studies with HEMGENIX®. Safety and efficacy of this medicinal product in these patients have not been established.

HIV positive patients

Limited clinical data are available in patients with controlled HIV infection treated with HEMGENIX®. The safety and efficacy in patients with HIV infection not controlled with anti-viral therapy, as shown by CD4+ counts ≤ 200/μL, was not established in clinical studies with HEMGENIX®.

Patients with active or uncontrolled chronic infections

There is no clinical experience with administration of HEMGENIX® in patients with acute infections (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic infections (such as active chronic Hepatitis B)(see section 4.3 Contraindications). It is possible that such acute or uncontrolled infections may affect the response to HEMGENIX® and reduce its efficacy and/or cause adverse reactions.

Use in hepatic impairment

The safety and efficacy of HEMGENIX® in patients with advanced hepatic impairment, including cirrhosis, advanced liver fibrosis (e.g. suggestive of or equal to METAVIR (Meta-analysis of Histological Data in Viral Hepatitis) Stage 3 disease or a liver elastography (FibroScan) score of ≥ 9 kPa), or uncontrolled Hepatitis B and C, has not been studied (see sections 4.3 Contraindications and 5.2 Pharmacokinetic properties).

Use in renal impairment

In the pivotal Phase 3 study, 8 of the 54 enrolled subjects had renal impairment. Seven subjects had mild and 1 subject had moderate renal impairment (see section 5.1 Pharmacodynamic properties – Clinical trials). All 8 subjects with renal impairment responded to HEMGENIX® treatment.

The safety and efficacy of HEMGENIX® in patients with severe renal impairment and end-stage renal disease has not been studied (see section 5.2 Pharmacokinetic properties).

Use in the elderly

Clinical studies with HEMGENIX® included 6 elderly patients with haemophilia B aged 68 to 75 years at time of enrolment. No meaningful differences in the safety and efficacy of HEMGENIX® were observed in these subjects compared to subjects aged 18 to 65 years (see section 5.1 Pharmacodynamic properties – Clinical trials).

Paediatric use

The safety and efficacy of HEMGENIX® in patients below 18 years of age have not been studied. No data are available.

Effects on laboratory tests

No data available. See Laboratory testing and monitoring for required laboratory testing.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

Hepatotoxic medicinal products or substances

Experience with use of this medicinal product in patients receiving hepatotoxic medications or using hepatotoxic substances is limited. Safety and efficacy of HEMGENIX® in these circumstances have not been established (see section 4.4 Special warnings and precautions for use).

Before administering HEMGENIX® to patients receiving potentially hepatotoxic medicinal products or using other hepatotoxic agents (including alcohol, potentially hepatotoxic herbal products and nutritional supplements) and when deciding on the acceptability of such agents after treatment with HEMGENIX®, physicians should consider that they may reduce the efficacy of HEMGENIX® and increase the risk for more serious hepatic reactions, particularly during the first year following HEMGENIX® administration (see section 4.4 Special warnings and precautions for use).

Vaccinations

Prior to HEMGENIX® infusion, ensure that the patient's vaccinations are up to date. The patient's vaccination schedule may need to be adjusted to accommodate concomitant immunomodulatory therapy (see section 4.4 Special warnings and precautions for use). Live vaccines should not be administered to patients while on immunomodulatory therapy.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No clinical studies have been performed to evaluate the effects of HEMGENIX® on impairment of human fertility.

An animal study examining potential effects on male fertility has been performed with a predecessor form of etranacogene dezaparvovec, rAAV5-hFIX, encoding wild type human factor IX rather than the Padua variant. Etranacogene dezaparvovec was derived from rAAV5-hFIX by the introduction of a 2 nucleotide change in the transgene for human factor IX.

Fertility was unaffected in male mice that were paired with untreated females 6 days after intravenous administration of rAAV5-hFIX at 2.3×10^{14} gc/kg (corresponding to approximately 10-times the clinical dose). No fertility study has been performed in female animals.

Use in pregnancy – Category B2

There are no clinical data available regarding HEMGENIX® use in pregnant women. No animal embryofetal development studies have been performed. HEMGENIX® should not be used during pregnancy.

Use in lactation

There are no data available regarding HEMGENIX® use in breast-feeding women. It is not known whether etranacogene dezaparvovec is excreted in human milk. HEMGENIX® should not be used during breast-feeding due to the unknown risk to the infant.

Contraception after administration in males

In clinical studies, after administration of HEMGENIX®, transgene DNA was temporarily detectable in semen (see section 5.2, sub-section HEMGENIX® vector DNA shedding).

For 12 months after administration of HEMGENIX®, treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception.

Males treated with HEMGENIX® must not donate semen to minimise the potential of paternal germline transmission (see section 4.4, sub-section Shedding).

In a study in male mice with rAAV5-hFIX (the predecessor form of etranacogene dezaparvovec), vector DNA was detected in reproductive organs and sperm following administration at approximately 10-times the clinical dose, but not in sired foetuses, indicating an absence of paternal germline transmission.

Women of childbearing potential

No data are available to recommend a specific duration of contraceptive measures in women of childbearing potential. Therefore, HEMGENIX® is not recommended in women of childbearing potential.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

HEMGENIX® has not been formally assessed for its effect on the ability to drive and use machines. However, some of the effects mentioned in section 4.8 Adverse effects (Undesirable effects) may temporarily affect the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Treatment-emergent adverse events

Across clinical studies (CT-AMT-061-01 and CT-AMT-061-02), all 57 subjects treated experienced at least 1 treatment-emergent adverse event (TEAE) during the Post-treatment follow-up period (**Table 2**). The most commonly reported TEAEs by preferred term, irrespective of investigator causality assessment were Arthralgia (36.8%), Headache (31.6%), Nasopharyngitis (26.3%), Fatigue (24.6%), and ALT Increased (21.1%).

Table 2: TEAEs irrespective of causality following HEMGENIX® treatment in ≥10% subjects

MedDRA System Organ Class (SOC)	Treatment-emergent Adverse Event (Preferred Term)	Subject numbers (%)	Number of TEAEs
Infections and infestations	Nasopharyngitis	15 (26.3)	20
	COVID-19	10 (17.5)	10
Nervous system disorders	Headache	18 (31.6)	35
Vascular disorders	Hypertension	7 (12.3)	7
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	7 (12.3)	7
	Cough	6 (10.5)	6
Gastrointestinal disorders	Toothache	7 (12.3)	11
	Diarrhoea	6 (10.5)	6
	Nausea	6 (10.5)	6
Musculoskeletal and connective tissue disorders	Arthralgia	21 (36.8)	37
	Back pain	11 (19.3)	14
	Pain in extremity	9 (15.8)	10
General disorders and administration site conditions	Fatigue	14 (24.6)	17
	Influenza-like illness	7 (12.3)	12
Investigations	Alanine aminotransferase increased	12 (21.1)	14
	Aspartate aminotransferase increased	9 (15.8)	10
	Blood creatine phosphokinase increased	9 (15.8)	12

Hepatic laboratory abnormalities

Table 3 describes hepatic laboratory abnormalities following administration of HEMGENIX®. ALT increases are further characterised, as they may be accompanied by decreased factor IX activity and may indicate the need to initiate corticosteroid treatment (see section 4.4).

Table 3: Hepatic laboratory abnormalities in patients administered 2 x 10^{13} gc/kg body weight HEMGENIX® in clinical studies

Laboratory Parameter Increases[a]	Number of patients (%) N = 57
ALT increases > ULN[b]	**23 (40.4%)**
> ULN – 3.0 x ULN[c]	17 (29.8%)
> 3.0 – 5.0 x ULN[d]	1 (1.8%)
> 5.0 – 20.0 x ULN[e]	1 (1.8%)
AST increases > ULN[b]	**24 (42.1%)**
> ULN – 3.0 x ULN[c]	19 (33.3%)
> 3.0 – 5.0 x ULN[d]	4 (7.0%)
Bilirubin increases > ULN[b]	**14 (24.6%)**
> ULN – 1.5 x ULN[c]	12 (21.1%)

Abbreviations: ULN = Upper Limit of Normal; CTCAE = Common Terminology Criteria for Adverse Events

[a]Highest post-dose CTCAE Grades of values are presented

[b]Not all patients with laboratory abnormality >ULN reached CTCAE Grade 1 due to elevated baseline levels

[c]CTCAE Grade 1

[d]CTCAE Grade 2

[e]CTCAE Grade 3

Summary of adverse drug reactions

The safety of HEMGENIX® was evaluated in 57 subjects from 2 clinical studies (CT-AMT-061-01 and CT-AMT-061-02). The most frequently reported adverse drug reactions in clinical studies related to HEMGENIX® were headache (18/57 subjects (31.6%)), ALT elevations (13/57 subjects (22.8%)), AST elevations (10/57 subjects (17.5%)), and influenza-like illness (8/57 subjects (14%)).

Table 4 shows the overview of adverse reactions from clinical studies with HEMGENIX®, categorised according the MedDRA System Organ Class (SOC), Preferred Term Level and frequency per patient. From a total of N=57 subjects treated with HEMGENIX® (n=3 subjects from a Phase 2b and n=54 subjects from a Phase 3 clinical study), the identified adverse reactions are listed based on the following convention for frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency category, adverse reactions are presented in order of decreasing frequency.

Table 4: Adverse drug reactions (ADRs) obtained from clinical studies with HEMGENIX®

MedDRA System Organ Class (SOC)	Adverse Reaction (Preferred Term)	Frequency per subject
Nervous system disorders	Headache	Very common
	Dizziness	Common
Gastrointestinal disorders	Nausea	Common
General disorders and administration site conditions	Influenza-like illness	Very common
	Malaise	Common
	Fatigue	Common
Investigations	Alanine aminotransferase increased	Very common
	Aspartate aminotransferase increased	Very common
	C-reactive protein increased	Very common
	Blood creatine phosphokinase increased	Common
	Blood bilirubin increased	Common
Injury, poisoning and procedural complications	Infusion related reaction (Hypersensitivity, Infusion site reaction, Dizziness, Eye pruritus, Flushing, Abdominal pain upper, Urticaria (Hives), Chest discomfort, Pyrexia (Fever))	Very common*

*Individual symptoms occurred in 1 or 2 subjects (incidence 1.8 to 3.5%) within 24 hours post-dose.

Description of selected adverse reactions

Infusion related reactions

In the clinical studies with HEMGENIX®, infusion-related reactions of mild to moderate severity have been observed in 7/57 subjects within 24 hours post-dose. The infusions were temporarily interrupted in 3 subjects and resumed at a slower infusion rate after treatment

with antihistamines and/or corticosteroids. In 1 subject, infusion was stopped and not resumed (see section 5.1 Pharmacodynamic properties – Clinical trials).

Immune-mediated transaminitis

In the clinical studies, an ALT increase occurred in 13 out of 57 subjects. The onset of ALT elevations ranged from day 22 to 787 post-dose. Nine out of the 13 subjects with ALT elevations received a tapered course of corticosteroid. The mean corticosteroid treatment duration for those subjects was 81.4 days. Nine of the 13 subjects with an ALT elevation also experienced AST elevations. All treatment-emergent adverse events of elevated ALTs were non-serious and resolved within 3 to 127 days.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There are no clinical study data regarding overdose with HEMGENIX®.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Etranacogene dezaparvovec, HEMGENIX® is a gene therapy designed to introduce a copy of the human factor IX gene into hepatocytes to address the root cause of the haemophilia B disease. HEMGENIX® consists of a codon-optimised coding DNA sequence of the Padua variant of human factor IX (hFIXco-Padua), under control of the liver-specific LP1 promoter, encapsulated in a non-replicating recombinant adeno-associated viral vector of serotype 5 (AAV5). The Padua variant differs from the wild type human factor IX by 1 amino acid (R338L); this substitution confers markedly increased factor IX activity.

Following 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, restoring the haemostatic potential and limiting bleeding episodes and the need for exogenous factor IX treatment.

Clinical trials

The safety and efficacy of HEMGENIX® was evaluated in 2 prospective, open-label, single-dose, single-arm studies, a Phase 2b (CT-AMT-061-01) study performed in the US and a Phase 3 multi-national study (CT-AMT-061-02) performed in the US, UK and EU. Both studies enrolled adult male patients (body weight range: 58 to 169 kg) with moderately severe or severe haemophilia B (N=3 in Phase 2b and N=54 in Phase 3), who received a single intravenous dose of 2×10^{13} gc/kg body weight of etranacogene dezaparvovec and entered a follow-up period of 5 years.

Phase 3 study (CT-AMT-061-02) – the HOPE B study

In the ongoing pivotal Phase 3 study, a total of N=54 patients aged 19 to 75 at enrolment (n = 6 >65 years) with moderately severe or severe haemophilia B completed a ≥6-month observational lead-in period with standard of care routine factor IX prophylaxis after which subjects received a single intravenous dose of HEMGENIX®. Post-treatment follow-up visits occurred regularly, with 52/54 subjects completing at least 24 months of follow-up. One subject with numerous cardiovascular and urologic risk factors, aged 75 at screening, died of urosepsis and cardiogenic shock at month 15 post-dose (at age 77 years), an event considered unrelated to treatment by the investigator. One subject with a pre-existing neutralising antibody titre of 1:3212 received full treatment, but remained on routine prophylaxis and withdrew from the study after 24 months post-treatment. The remaining 52/54 subjects continue follow-up for a total of 5 years post-dose. Of these, 1 subject received a partial dose (10%) of HEMGENIX® due to an infusion related reaction during infusion.

The primary efficacy endpoint for the Phase 3 study was to assess the annualised bleeding rate (ABR) for non-inferiority between month 7 to 18 post-dose after establishment of stable factor IX expression by month 6, compared to the observational lead-in period. For this purpose, all bleeding episodes, regardless of investigator assessment, were considered. The primary efficacy analysis demonstrated non-inferiority and a key secondary analysis showed superiority of HEMGENIX® to continuous routine factor IX prophylaxis. The ABR for all types of bleeds after stable factor IX expression decreased in the Full Analysis Set (FAS; N=54) from a mean of 4.19 for the lead-in period to a mean of 1.51 (1-sided p = 0.0002) in the months 7-18 post-dose (see **Table 5**). These results demonstrated an overall ABR reduction by 64% (95% Confidence Interval (CI): 36%, 80%, 1-sided p = 0.0002) from the lead-in to the 7-18 month post-treatment period.

Severe or very severe bleeding episodes were reported during the lead-in period in 18.5% and 5.6% of subjects, respectively, and decreased during month 7-18 to 13% and 3.7% of subjects

for severe and very severe bleeds, respectively. The ABRs by subtype of bleeding episodes during month 7-18 were significantly reduced after HEMGENIX® treatment compared to the lead-in period. For spontaneous bleeding episodes the ABR decreased from 1.52 to 0.44 and the rate ratio of post-treatment/lead-in period was 0.29 (95% Wald CI: 0.12, 0.71; p = 0.0034). For joint bleeding episodes the ABR decreased from 2.35 to 0.51 and the rate ratio of post-treatment/lead-in period was 0.22 (95% Wald CI: 0.10, 0.46; p <0.0001).

Table 5: Total bleeding events and ABRs

Number	≥6-month Lead-in period FAS (N=54)	7-18 months Post-dose FAS (N=54)
Subjects with bleeds	40 (74.1%)	20 (37.0%)
Subjects with zero bleeds	14 (25.9%)	34 (63.0%)
Any bleeds	136	54
Mean adjusted* ABR** (95% CI) for any bleeds	4.19 (3.22, 5.45)	1.51 (0.81, 2.82)
ABR** ratio (post-dose / lead-in) 2-sided 95% Wald CI 1-sided p-value***	N/A	0.36 (0.20, 0.64) p = 0.0002

Abbreviations: ABR = annualised bleeding rate; FAS = Full Analysis Set including all 54 subjects dosed; CI = confidence interval; N/A = Not Applicable

*Adjusted: Adjusted ABR and comparison of ABR between lead-in and post-treatment period was estimated from statistical modelling (i.e. from a repeated measures generalised estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate.)

**The ABR was measured from month 7 to 18 after HEMGENIX® infusion, ensuring this period represented steady-state factor IX expression from the transgene.

***1-sided p-value ≤0.025 for post-treatment/lead-in <1 was regarded as statistically significant.

After a single dose of HEMGENIX®, clinically relevant increases in factor IX activity were observed as measured by the one-stage (aPTT-based) assay (see **Table 6**).

Table 6: Factor IX activity at 6, 12, 18 and 24 months (FAS; one-stage (aPTT-based) assay)

	Baseline[1] (N=54)[#]	6 months post-dose (N=51[#])	12 months post-dose (N=50[#])	18 months post-dose (N=50[#])	24 months post-dose[***] (N=50[#])
Mean % (SD)	1.19 (0.39)	38.95 (18.72)	41.48 (21.71)	36.90 (21.40)	36.66 (18.96)
Median % (min, max)	1.0 (1.0, 2.0)	37.30 (8.2, 97.1)	39.90 (5.9, 113.0)	33.55 (4.5, 122.9)	33.85 (4.7, 99.2)
Change from baseline LS mean (SE)[*] 95% CI 1-sided p-value[**]	N/A	36.18 (2.432) 31.41, 40.95 p <0.0001	38.81 (2.442) 34.01, 43.60 p <0.0001	34.31 (2.444) 29.52, 39.11 p <0.0001	34.13 (2.325) 29.57, 38.69 p <0.0001

Abbreviations: aPTT = activated Partial Thromboplastin Time; CI = confidence interval; FAS = Full Analysis Set including all 54 subjects dosed; LS = least squares; max = maximum; min = minimum; N/A = Not Applicable; SD = standard deviation; SE = standard error.

[1]Baseline: baseline factor IX activity was imputed based on a subject's historical haemophilia B severity documented on a case report form. If the subject had documented severe factor IX deficiency (factor IX plasma level <1%), their baseline factor IX activity level was imputed as 1%. If the subject had documented moderately severe factor IX deficiency (factor IX plasma level ≥1% and ≤2%,) their baseline factor IX activity level was imputed as 2%.

[#]Uncontaminated: the blood samples collected within 5 half-lives of exogenous factor IX use were excluded. Both the date and time of exogenous factor IX use and blood sampling were considered in determining contamination. Subjects with zero uncontaminated central laboratory post-treatment values had their change from baseline assigned to zero for this analysis, and had their post-baseline values set equal to their baseline value. Baseline factor IX was imputed based on subjects' historical haemophilia B severity documented on the case report form. The FAS included 1 subject who received only 10% of the planned dose, 1 subject who died at month 15 post-dose due to unrelated concomitant disease, 1 subject with a 1:3212 titre of pre-existing neutralising anti-AAV5 antibodies who did not respond to treatment and 1 subject with contamination with exogenous factor IX. Accordingly, the population data included 54 to 50 subjects with uncontaminated sampling.

[*]Least Squares Mean (SE) mean from repeated measures linear mixed model with visit as a categorical covariate.

[**]1-sided p-value ≤0.025 for post-treatment above baseline was regarded as statistically significant.

[***]For month 24, data was based on an ad-hoc analysis and the p-value was not adjusted for multiplicity.

Neutralising anti-AAV5 capsid antibodies were present in 21/54 (38.9%) subjects at baseline. At 18 months post-dose, mean factor IX activity was 31.14% and 39.87% for subjects with and without pre-existing neutralising anti-AAV5 antibodies, respectively, with LS mean increases from baseline of 26.83% (95% CI: 19.24, 34.41; 1-sided p <0.0001) and 38.72% (95% CI: 32.49, 44.95; 1-sided p <0.0001), respectively. However, no clinically meaningful correlation between an individual antibody titre of pre-existing anti-AAV5 antibodies with their factor IX activity at 18 months was identified.

In 1 subject (1/54) with a titre of 1:3212 for pre-existing anti-AAV5 antibodies at screening, no response to HEMGENIX® treatment was observed, with no factor IX expression and activity.

All subjects were on prophylactic factor IX replacement therapy prior to dosing with HEMGENIX®. The consumption of factor IX replacement therapy was significantly lower between month 7 and 18 following treatment with HEMGENIX® compared to standard of

care routine factor IX prophylaxis during the lead-in period, with a mean factor IX consumption decrease by 248,825 IU/ year / subject (96.7%; 1-sided p <0.0001). From day 21 up to month 18, 52 of 54 (96.3%) treated subjects remained free of continuous factor IX prophylaxis.

5.2 PHARMACOKINETIC PROPERTIES

Factor IX activity and factor IX protein

Clinically relevant and statistically significant increases in factor IX activity were observed after administration of HEMGENIX® (see section 5.1 Pharmacodynamic properties – Clinical trials). In the Phase 3 study, following a single dose of HEMGENIX®, the mean factor IX activity levels, as measured by one-stage (activated Partial Thromboplastin Time (aPTT)-based) testing gradually increased. The uncontaminated factor IX activity levels (excluding measurements within 5 half-lives of factor IX replacement therapy) achieved by subjects are provided in **Table 6** (see section 5.1 Pharmacodynamic properties – Clinical trials).

The time to onset of factor IX protein expression post-dose was detectable by first uncontaminated measurement at week 3, as measured in Phase 3 study (see section 5.1 Pharmacodynamic properties – Clinical trials). In general, although more variable, factor IX protein kinetic profile during the post-treatment period followed a trend similar to factor IX activity.

Absorption

As HEMGENIX® is administered intravenously, there are no relevant absorption data.

Distribution and Metabolism

The HEMGENIX®-derived factor IX protein produced in the liver is expected to undergo similar distribution and catabolic pathways as the endogenous native factor IX protein in people without factor IX deficiency.

The biodistribution of etranacogene dezaparvovec after intravenous administration was examined in mice and cynomolgus monkeys. Vector DNA level was highest in the liver in both species.

Excretion and Elimination

No specific radiolabel clinical studies for HEMGENIX® have been conducted. Vector DNA from HEMGENIX® administration is cleared in saliva, nasal secretions, urine and faeces.

HEMGENIX® vector DNA shedding

The pharmacokinetics of vector DNA shedding in blood and semen following HEMGENIX® administration was characterised in Phase 2b and Phase 3 studies.

In the Phase 2b study (N=3), patients achieved a status of no longer shedding, or absence of vector DNA, once vector DNA was below the limit of detection for at least 3 consecutive time points. Clearance of vector DNA from semen and blood was achieved in 2/3 subjects after 3 years post-dose. The earliest absence of vector DNA was achieved at 26.1 weeks post-dose in semen (mean 26.21; range: 26.1 to 26.3 weeks) and 31.1 weeks post-dose in blood (mean 54.71; range: 31.1 to 78.3 weeks). One of 3 subjects had positive blood testing results at 3 years post-dose.

In the Phase 3 study, the median time of observed maximum levels of vector DNA was 4 hours in blood (range: 3 to 7 hours) and 6 weeks in semen (range: 6 to 30 weeks) after HEMGENIX® administration (N=54 subjects). The earliest absence of vector DNA in blood was observed by week 17 (1/54; 1.9% of subjects). A total of 56% (30/54) of subjects reached absence of vector DNA from blood by month 24. The earliest absence of vector DNA in semen was observed by week 6 (1/54; 1.9% of subjects). A total of 69% (37/54) of subjects reached absence of vector DNA from semen by month 24. The median time to absence of vector DNA was 52.3 weeks in blood and 45.8 weeks in semen at 24 months post-dose.

Pharmacokinetics in special populations

Patients with hepatic impairment

In the Phase 3 study, subjects with varying degree of baseline liver steatosis, specifically the degree of hepatic steatosis with the Controlled Attenuation Parameter (CAP) score of ≥S2 (≥260 decibels/m) versus <S2 (<260 decibels/m) were compared. Subjects with (CAP) scores of ≥S2 (≥260 decibels/m; n=12; range: 262 to 400)), <S2 (<260 decibels/m; n=28; range: 100 to 259) and missing score (n=14) showed no clinically relevant different factor IX activity levels between the groups following HEMGENIX® administration.

Patients with advanced liver impairment and advanced fibrosis (elastography of e.g. ≥9 kPA, or suggestive of or equal to METAVIR Stage 3 disease) were not studied (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Patients with renal impairment

In the Phase 3 study, subjects with mild renal impairment (creatinine clearance (CLcr) = 60 to 89 mL/min defined by Cockcroft-Gault equation, n=7) were observed to have numerically higher factor IX activity (up to 37% relative difference) compared to those with normal renal

function (CLcr ≥90 mL/min; n=45) across different time points following etranacogene dezaparvovec administration. One subject with moderate renal impairment (CLcr = 30 to 59 mL/min) in this study had similar factor IX activity as subjects with normal renal function.

HEMGENIX® was not studied in patients with severe renal impairment (CLcr = 15 to 29 mL/min) or end-stage renal disease (CLcr <15 mL/min) (see section 4.4 Special warnings and precautions for use).

Paediatric population

HEMGENIX® has not been studied in patients below 18 years of age. No data are available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxic risk was evaluated with the predecessor form of etranacogene dezaparvovec, rAAV5-hFIX. The integration site analysis in host genomic DNA was performed on liver tissue from mice and cynomolgus monkeys injected with rAAV5-hFIX up to a dose of 2.3×10^{14} gc/kg body weight, corresponding to approximately 10-fold the clinical dose in humans. The retrieved rAAV5-hFIX vector DNA sequences represented almost exclusively episomal forms that were non-integrated into the host DNA. The remaining low level of integrated rAAV5-hFIX DNA was distributed throughout the host genome with no preferred integration next to or within genes associated with mediation of malignant transformation in humans and no sign of clonal expansion seen.

Carcinogenicity

No animal carcinogenicity studies have been conducted with etranacogene dezaparvovec.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sucrose
Polysorbate 20
Potassium chloride
Monobasic potassium phosphate
Sodium chloride
Dibasic sodium phosphate
Hydrochloric acid (pH adjustment)
Water for Injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, with the exception of 0.9% normal saline solution used for HEMGENIX® dilution prior to administration (see section 4.2 Dose and method of administration).

The compatibility of HEMGENIX® was established for intravenous infusion lines with integrated in-line 0.2 µm filters made out of polyethersulfone (PES).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After dilution

HEMGENIX® contains no antimicrobial preservative.

To reduce the microbiological hazard, use the product as soon as possible after the HEMGENIX® dose has been prepared. Once diluted with 0.9% normal saline (see section 4.2 Dose and method of administration), HEMGENIX® can be stored at room temperature (15°C to 25°C) in the infusion bag protected from light. The administration of HEMGENIX® to the patient should be completed within 6 hours after the dose is prepared.

The stability after dilution was established for Polyethylene/Polypropylene (PE/PP) copolymer, Polyvinyl chloride (PVC)-free infusion bags with 0.9% normal saline.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator at 2°C to 8°C. Do not freeze. Store in the original package to protect from light. Do not use HEMGENIX® after the expiry date.

For storage conditions after dilution of the medicinal product, see section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

HEMEGNIX® is supplied as a 10 mL solution in a glass vial with a latex free rubber stopper and aluminium seal with a flip-off cap.

The total number of vials in each finished pack is prepared for the dosing requirement for an individual patient based on their body weight, and is provided on the package (see section 4.2 Dose and method of administration and **Table 7**). Each 10 mL vial corresponds to a 5 kg patient body weight range.

Table 7: HEMGENIX® finished pack configurations

Patient body weight range (kg)	Total volume (mL)	Total vials per carton
46-50	100	10
51-55	110	11
56-60	120	12
61-65	130	13
66-70	140	14
71-75	150	15
76-80	160	16
81-85	170	17
86-90	180	18
91-95	190	19
96-100	200	20
101-105	210	21
106-110	220	22
111-115	230	23
116-120	240	24
121-125	250	25
126-130	260	26
131-135	270	27
136-140	280	28
141-145	290	29
146-150	300	30
151-155	310	31
156-160	320	32
161-165	330	33
166-170	340	34
171-175	350	35
176-180	360	36
181-185	370	37
186-190	380	38
191-195	390	39
196-200	400	40
201-205	410	41
206-210	420	42
211-215	430	43
216-220	440	44

Patient body weight range (kg)	Total volume (mL)	Total vials per carton
221-225	450	45
226-230	460	46
231-235	470	47
236-240	480	48

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

HEMGENIX® contains a genetically modified organism (GMO). Unused medicinal product and all waste products that have been in contact with the GMO must be handled and disposed of as potentially infectious waste in a container dedicated to GMO in compliance with the local institutional biosafety guidelines for GMO or biohazardous waste, as appropriate.

Non-disposable materials should be cleaned with a 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. Contact surfaces should be disinfected with a similar disinfectant.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number

2156583-26-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

TBD

10 DATE OF REVISION

Not applicable

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	Initial version