HEMGENIX
Operational Guidance

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CSL Behring
Medical Affairs

Introduction

The information presented in this manual is intended to illustrate the clinical pathway for gene therapy, while also offering providers, who intend to both administer and refer patients to administration centers, insights into guidance that is specific to HEMGENIX (etranacogene dezaparvovec), an approved gene therapy for patients with hemophilia B.

In addition to information that directly aligns with the Health Canada approved Product Monograph, this manual also incorporates important elements for health care providers to consider as they develop center-specific protocols and sample worksheets that can serve as templates and be tailored to meet center-specific needs.

Contents

Overview of Gene Therapy

Introduction

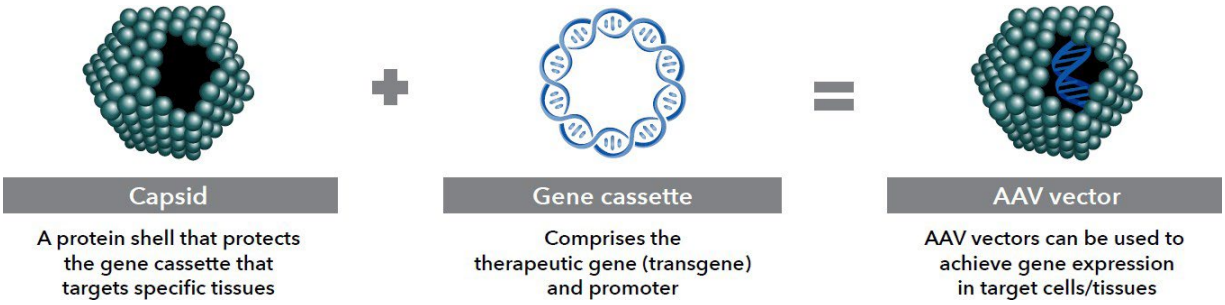
This section aims to provide some basic background information about gene therapy as it relates to Hemophilia B, with specific reference to the structure of HEMGENIX.

What is gene therapy?

- Gene therapy is defined as a technique that modifies a person's gene to treat a disease. Gene therapies work through various approaches, including introducing a functional gene or inactivating/editing a disease-causing gene[1,2]
- Gene therapy approaches for inherited monogenic diseases, like Hemophilia B, have predominantly focused on delivery of a functional gene using a viral vector[3]
- Viral vectors can be divided into predominantly integrating (retrovirus, lentivirus) and predominantly non-integrating (adenovirus and adeno-associated virus [AAV]) vectors[4]
- In AAV-based gene transfer therapy, a working gene is inserted into an AAV vector[5-7]
  - An AAV vector protects and delivers the new gene to its destination through a one-time infusion
  - A protein coating on the vector acts like a delivery address so the gene goes where it's needed
  - For hemophilia B, the working gene needs a vector that targets the liver
  - Once the new gene reaches its destination, the body can begin to produce the missing protein for hemophilia B, which is factor IX

How does AAV-based gene therapy work?

- In AAV vector-based gene therapy, the following modifications have been made to the AAV vector genome:[8,9]
  - Replication genes have been removed, rendering the virus replication-deficient
  - Genes encoding AAV capsid proteins have been replaced with a gene cassette containing the tissue-specific promoter and therapeutic gene of interest
  - AAV vector in the form of an empty capsid containing a gene cassette is used as a carrier for gene delivery to the target cells (as illustrated below). AAV vectors have a packing capacity of ≤5 kb, limiting the size of the expression cassette, and therefore the size of the transgene that can be expressed.[10,11] It's for this reason that gene therapy for Hemophilia A requires significant modification of the expression cassette, as *F8* cDNA (7 kb) is much larger than *F9* cDNA (1.6 kb)[12]
- After infusion, the AAV vector delivers the therapeutic gene to the cell nucleus, allowing for long-term gene expression from the gene cassette[8]
- The gene cassette exists in the nucleus primarily in a form of stable episomal DNA and generally does not integrate into the patient's genome[9,10,13,14]

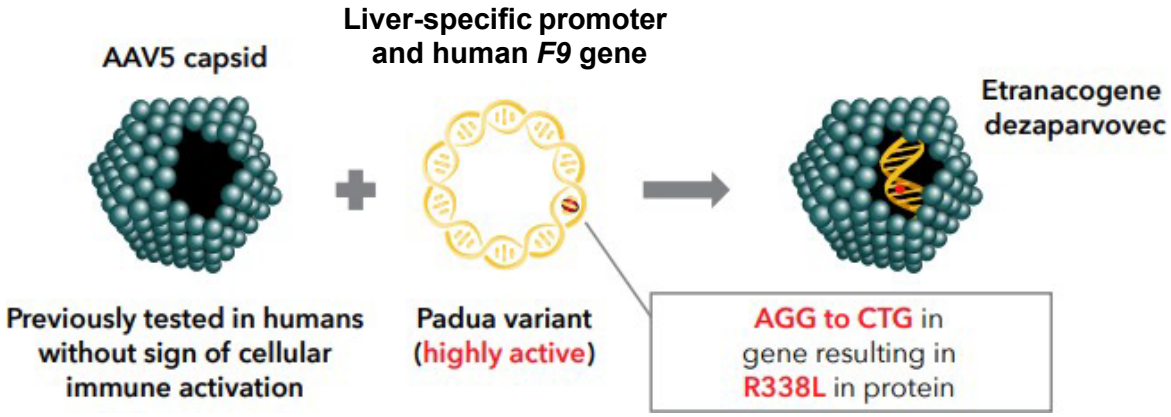


How does gene therapy work for Hemophilia B?

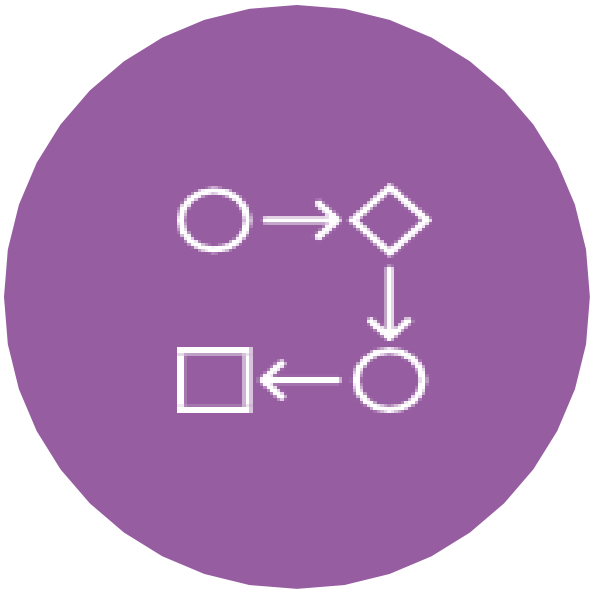
- Hemophilia B is caused by mutations in a single Factor IX gene, which is small enough to fit inside the AAV vector[11,12,15]
- Naturally occurring AAVs have serotype-specific tropisms for specific cells and tissues, including the liver, where Factor IX is produced[16,17]
- Modified transgenes have been used in AAV expression cassettes that encode proteins with greater activity compared with wild type (such as the Padua variant)[18-20]
- The Padua variant is a naturally occurring gain-of-function mutation in the catalytic domain of Factor IX (amino acid arginine 338 changed to leucine) that results in a 5- to 10-fold increase in specific Factor IX activity compared with wild type[20]

Structure of HEMGENIX

HEMGENIX is an AAV-based gene therapy consisting of a codon-optimized coding DNA sequence of the gain-of-function Padua variant of human Factor IX (variant R338L), under control of a liver-specific LP1 promoter, encapsulated in a non-replicating recombinant AAV vector of serotype 5 (AAV5).

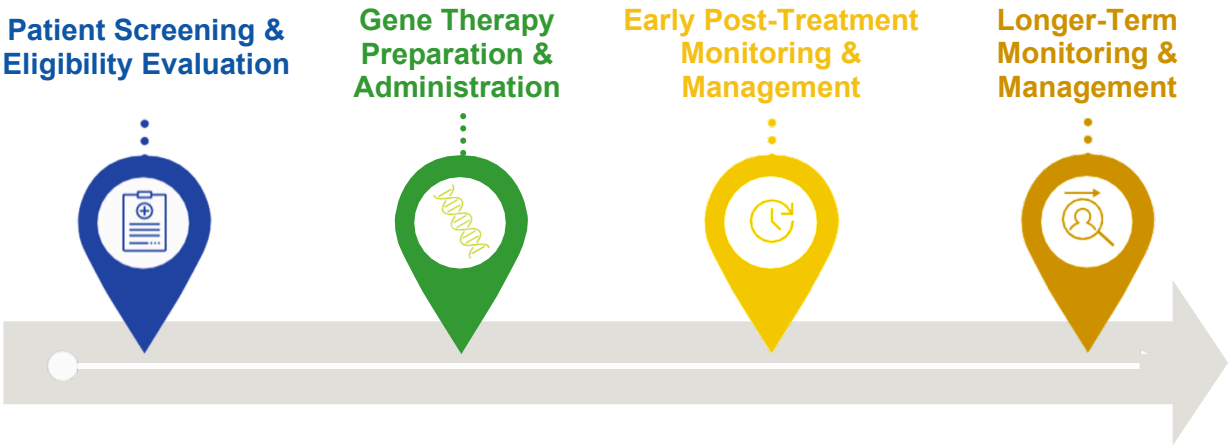


Steps of the Gene Therapy Process



Introduction

- Practical considerations are required for the clinical implementation of gene therapies such as HEMGENIX
- While the optimum care model for the administration and follow-up of gene therapy is yet to be fully determined, information and steps performed in clinical trials provide us with some information that can be translated and followed clinically
- Currently, gene therapy expertise is localized to certain centers, and education will be required to disseminate knowledge across the hemophilia community[3]
- CSL Behring has garnered input and feedback from many of these experts about their experience towards development of a gene therapy process operationalization (GTPO) model to organize the information and guidance contained in this manual
- The GTPO model describes practical clinical considerations across four main steps:



General considerations for gene therapy center preparedness

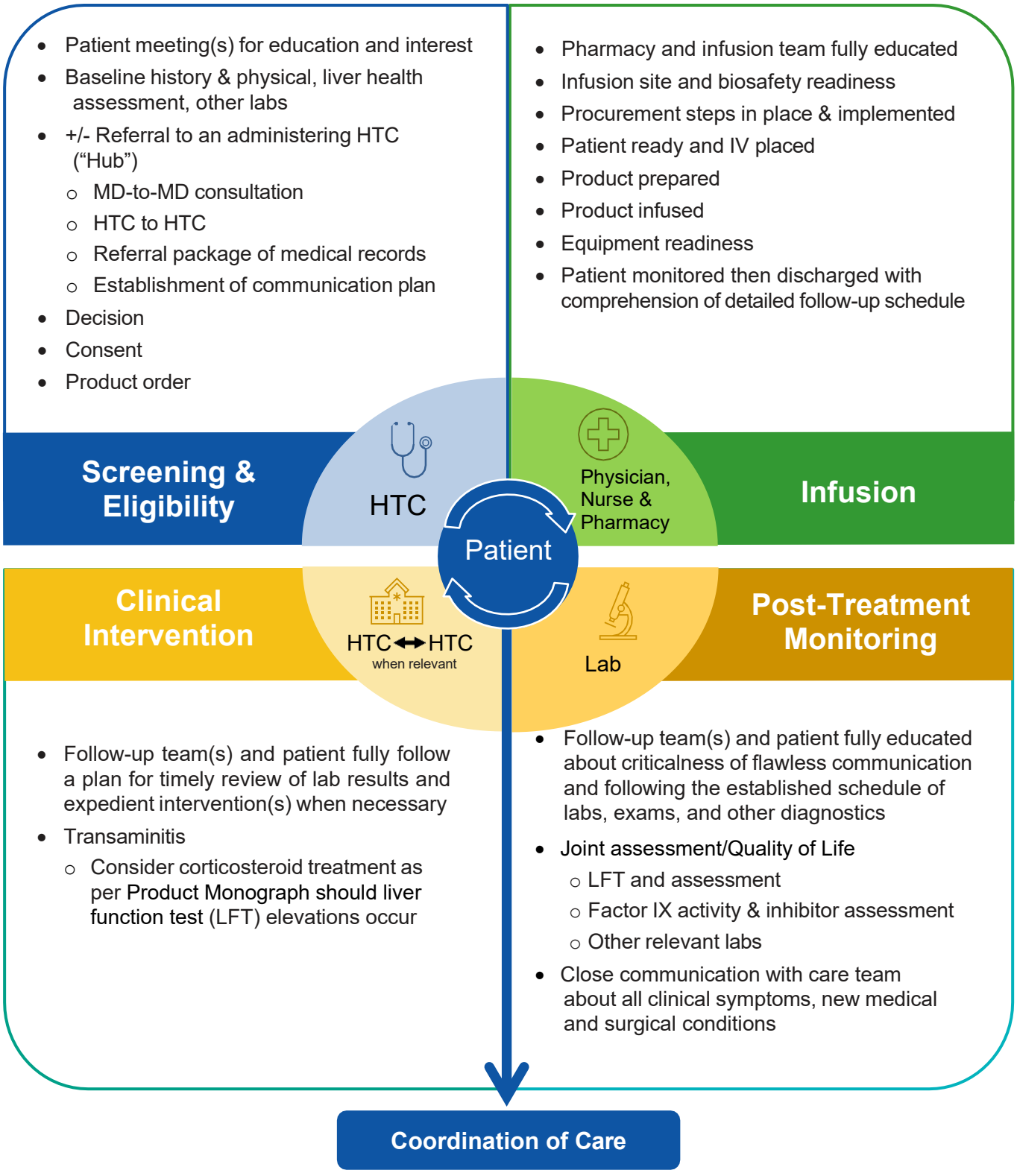
- All Hemophilia Treatment Center (HTC) teams must fully understand all aspects of each of the gene therapy process steps in order to prepare team members and plan clinical operations to safely and appropriately implement the steps in a clinical setting with commercially approved products

Main elements of site preparedness

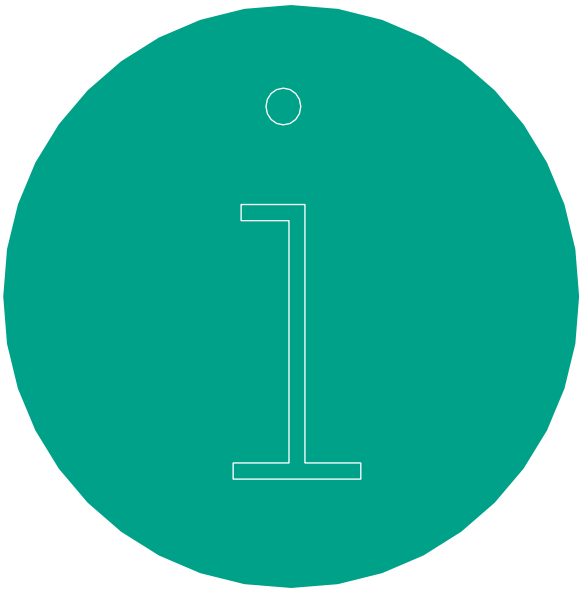
- Establish the clinical team and roles of each team member
- Identify the site for infusion
- Partner with pharmacy and other relevant departments involved in approving (Pharmacy and Therapeutics Committee), receiving, and handling gene therapy
- Implement gene therapy education and training for the HTC staff and patients, as well as other internal stakeholders
- Develop protocols for patient eligibility, evaluation, infusion (including biosafety considerations, e.g., sterile technique, containment, spill management), and short/long-term monitoring and management
- Assess and plan communication methods between internal partners (including Hepatologist, Pharmacist, Nursing, Psychologist, Social Worker, Physiotherapy), patients, and outside HTCs

Coordination of care

Throughout the clinical journey of gene therapy, it will be important to coordinate the care between multiple providers within the HTC as well as between different HTCs in the case of a patient referral. This schematic is intended to outline some of the areas where this coordination will be essential to ensure an optimal outcome for the patient.



HEMGENIX
Product Monograph



Indication and usage

HEMGENIX (etranacogene dezaparvovec) is indicated for treatment of adults (aged 18 years of age or older) with Hemophilia B (congenital Factor IX deficiency) who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

There is no clinical experience of HEMGENIX use in patients with mild or moderate Hemophilia B (FIX activity > 2%).

Aim

The aim of HEMGENIX therapy is to reduce the frequency of bleeding episodes and the need for Factor IX replacement therapy.

Description

HEMGENIX is an AAV vector-based gene therapy for intravenous infusion after dilution. HEMGENIX is a non-replicating recombinant AAV5 containing a codon-optimized DNA sequence of the gain-of-function Padua variant of human Factor IX (variant R338L), under control of a liver-specific promotor 1 (LP1).

Mechanism of action

HEMGENIX is an AAV serotype 5 (AAV5)-based gene therapy designed to deliver a copy of a gene encoding the Padua variant of human coagulation Factor IX (hFIX-Padua). Single intravenous infusion of HEMGENIX results in cell transduction and increase in circulating Factor IX activity in patients with Hemophilia B.

Following single intravenous infusion, HEMGENIX enters cells of the body, where the vector DNA resides almost exclusively in episomal form. After transduction, HEMGENIX directs liver-specific expression of Factor IX-Padua protein using a liver-specific promoter (LP1). As a result, HEMGENIX helps to restore circulating Factor IX procoagulant activity of Hemophilia B patients and their hemostatic potential, which limits bleeding episodes and the need for exogenous Factor IX treatment.

Dosage forms and strengths

The recommended dose of HEMGENIX is 2×10^{13} genome copies (gc) per kilogram (kg) of body weight (or 2 mL/kg body weight) administered as an intravenous infusion after dilution with 0.9% sodium chloride solution (normal saline).

HEMGENIX:

- Is a suspension for intravenous (IV) infusion after dilution
- Is provided as a customized kit containing 10 to 48 vials in each kit, constituting a dosage unit based on the patient's body weight
- Has a nominal concentration of 1×10^{13} gc/mL, and each vial contains an extractable volume of not less than 10 mL
- The total number of vials in each pack corresponds to the dosing requirement for the individual patient, depending on the patient's body weight, and is provided on the package

HEMGENIX IMPORTANT SAFETY INFORMATION

Warning and Precautions

General

Shedding

Shedding of HEMGENIX vector DNA will occur in blood, feces and semen of patients receiving HEMGENIX. Since some patients have detectable viral/transgene DNA detected in semen between 1 to 2 years following administration of HEMGENIX, barrier contraception is recommended for 2 years for males and their female partners of childbearing potential.

Blood, organ, and tissue donation

Patients treated with HEMGENIX should not donate blood, or organs, tissues and cells for transplantation to minimize the risk of exposure to non-target individuals. Caregivers should be advised on the proper handling of waste material generated from contaminated medicinal ancillaries during HEMGENIX use.

Driving and Operating Machinery

Patients treated with HEMGENIX may experience dizziness, fatigue, headaches, chest tightness and abdominal pain shortly after administration of HEMGENIX that may affect their ability to drive and use machines. Patients should not drive or use machines until symptoms resolve.

Hematologic

Risk of Thromboembolic Events

In clinical studies with HEMGENIX, treatment-related thromboembolic events were not reported and there was no evidence of supraphysiological FIX activity occurring in any patient. Restoration of Factor IX activity following administration of HEMGENIX, which encodes for a hyperactive Factor IX variant (Padua), may give rise to the potential risk for thromboembolic events. This potential risk is increased in Hemophilia B patients with pre-existing risk factors for thromboembolic events such as a history of cardiovascular disease, arteriosclerosis, hypertension, diabetes, and advanced age.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Hemophilia B patients with ALT, AST, total bilirubin and ALP > 2X upper limit of normal (ULN), 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 or C were excluded from clinical studies with HEMGENIX. There should be careful consideration before administering HEMGENIX to these patients.

Intravenous administration of a liver-directed AAV vector may potentially lead to liver transaminase elevations (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. Some transaminase elevations resolved spontaneously while others required administration of a corticosteroid taper to normal levels after a period of up to several weeks. Patients requiring treatment with corticosteroids following administration of HEMGENIX had numerically lower transgene FIX activity compared to patients who were not treated with corticosteroids.

To mitigate the risk of potential hepatotoxicity, transaminases should be closely monitored at least 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.

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.

It is recommended to advise patients treated with HEMGENIX to avoid, if possible, concomitant use

of hepatotoxic medication or potential hepatotoxic agents (including potentially hepatotoxic herbal products, nutritional supplements, and alcohol) due to the risk of potential loss or decrease in efficacy and more serious hepatic reactions.

Hepatocellular carcinogenicity

HEMGENIX is composed of a non-replicating AAV5 vector whose DNA remains largely in episomal form although DNA integration events have been reported in non-clinical and clinical studies. Vector integration into human genome, expected to occur at low frequency, may potentially result in insertional mutagenesis that could contribute to the development of malignancies. HEMGENIX-associated clonal expansion or carcinogenicity was not observed in preclinical or clinical studies. One patient with pre-existing risk factors for developing hepatic cancer developed a hepatocellular carcinoma following treatment with HEMGENIX, which was assessed as not likely related to the gene therapy based on vector integration site analyses and whole genome sequencing (where vector DNA was estimated to be integrated in < 0.03% of tumour cells).

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 in the 5 years following administration.

Immune

Immune-mediated neutralization of the AAV5 vector capsid

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

In the clinical studies with HEMGENIX, patients were not excluded based on pre-existing AAV5-neutralizing antibodies and the patient sub-group with detectable pre-existing neutralizing AAV5 antibodies had a mean Factor IX activity that was lower compared to that patient sub-group without detectable pre-existing neutralizing AAV5 antibodies. However, both patient groups, with and without detectable pre-existing neutralizing AAV5 antibodies, demonstrated an improved hemostatic protection compared to the standard of care Factor IX prophylaxis, except for one patient with a very high pre-existing neutralizing AAV5 titer who had no Factor IX transgene activity and was required to resume prophylactic treatment with exogenous Factor IX. Based on information obtained from the Phase 3 CT-AMT-061-02 clinical study, a threshold for an acceptable AAV5-neutralizing titer has been established to screen patients for eligibility to receive HEMGENIX.

Infusion-related reactions

Serious infusion-related reactions, including hypersensitivity reactions and anaphylaxis, can occur during and immediately following HEMGENIX administration. Symptoms may include chest tightness, headaches, abdominal pain, light-headedness, flu-like symptoms, shivering, flushing, rash, and hypertension. Closely monitor patients for signs or symptoms of infusion reactions throughout the infusion period and for at least 3 hours after end of infusion. In the event of an infusion reaction during administration, the infusion may be slowed or stopped. If the infusion is stopped, restart at a slower rate when the infusion reaction has resolved. Consider treatment with a corticosteroid or antihistamine for management of an infusion reaction.

In clinical studies with HEMGENIX in adult patients, three individuals had their infusions temporarily interrupted and resumed at a slower infusion rate. One individual who had their infusion stopped due to a serious hypersensitivity reaction did not resume treatment and had no measurable response to therapy.

Monitoring and Laboratory Tests

After HEMGENIX administration, a patient's Factor IX activity should be regularly monitored.

The activated partial thromboplastin time (aPTT)-based one-stage clotting assay (OSA) may produce variable results between laboratories for determining Factor IX activity and this can be affected by the type of aPTT reagent, laboratory, equipment and the reference standard used in the assay. This is important when considering changing the laboratory, equipment and/or reagents used in the assay.

Therefore, the same assay, laboratory, equipment and reagents are recommended to be used to monitor each patient's Factor IX activity over time.

The results of Factor IX activity tests are lower if measured with the two-stage chromogenic substrate assay (CSA) compared to the aPTT one-stage assay. In the clinical efficacy study with HEMGENIX, the post-dose Factor IX activity measured with CSA gave results that were approximately 50% lower (the mean CSA to aPTT one-stage Factor IX activity ratio ranging from 0.41 to 0.55).

Monitor patients through appropriate clinical observations and laboratory tests for the development of inhibitors to Factor IX after HEMGENIX administration. Perform an assay that detects Factor IX inhibitors if bleeding is not controlled, or plasma Factor IX activity levels decrease. If Factor IX activity decreases in the absence of FIX inhibitors, then loss of transgene expression in the liver should be suspected.

Reproductive Health: Female and Male Potential

Fertility

No clinical studies have been performed to evaluate the effects of HEMGENIX on impairment of human fertility. Vector DNA in some hemophilia B patients has been detected up to 2 years following infusion of HEMGENIX, clinical significance is unknown. It is recommended that male hemophilia B patients and their female partners of childbearing potential use barrier contraception for 2 years following infusion of HEMGENIX.

- HEMGENIX is for single-use intravenous infusion only.
- **Contraindications:** HEMGENIX is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- **For complete prescribing details, Please consult the Product Monograph for HEMGENIX.**

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at AdverseReporting@CSLBehring.com and visit Health Canada's website on Adverse Reaction Reporting (canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or calling toll-free at 1-866-234-2345.

Screening and Evaluation

Introduction

The first step in the patient-provider journey of gene therapy is the screening and eligibility evaluation. This includes gene therapy discussion, clinical eligibility evaluation, and an informed decision.

An important part of this step involves discussions with the patient to gauge their interest and assess their understanding of gene therapy as a treatment option. For most patients, this process is quite different from the hemophilia care to which they've become accustomed; therefore, it is crucial to ensure they fully understand the entirety of the process and all it may entail. Once a patient has demonstrated full understanding and interest in gene therapy, an evaluation to assess other diagnostic criteria necessary for eligibility (including blood work and radiology) should be completed.

A holistic evaluation may take place over time, include many different providers such as social workers, nurses, and physicians, and even involve different HTC. Therefore, it is imperative to maintain an open line of communication and coordination between the patient and provider(s) to ensure an optimal outcome.

This section provides some topics to consider when having discussions with patients as well as the laboratory and radiologic assessment that is minimally required in accordance with the HC-approved Product Monograph to complete the evaluation. Additional diagnostic workup may be required based on provider discretion. A comprehensive review of all relevant information is necessary when reaching a decision point with the patient.

Gene therapy discussion topics

- What gene therapy is and how it works
- Rationale for gene therapy as a treatment option for Hemophilia B
- Available gene therapy products
- Clinical trial results: efficacy and safety
- Benefits and risks as well as knowns and unknowns of gene therapy
- Overall gene therapy process steps and logistics
- Eligibility criteria and required diagnostics
- Patient expectations and commitment
- Provide any new information discovered and their long-term implications

Eligibility evaluation

- Medical history
- Physical exam
- Hemophilia history & baseline labs
- Factor IX-inhibitor titer test
- Liver health history & assessment
- Psychosocial assessment (see appendix for how to access NBDF Psychosocial template)
- Family Physician connection for communication plan
- Ensure cultural and language barriers are eliminated (e.g., cultural competency training, translators) so everyone has equal access to gene therapy
- Ensure patient was given opportunity to meet with a social worker or psychosocial support worker at least once during the gene therapy offering process

Decision

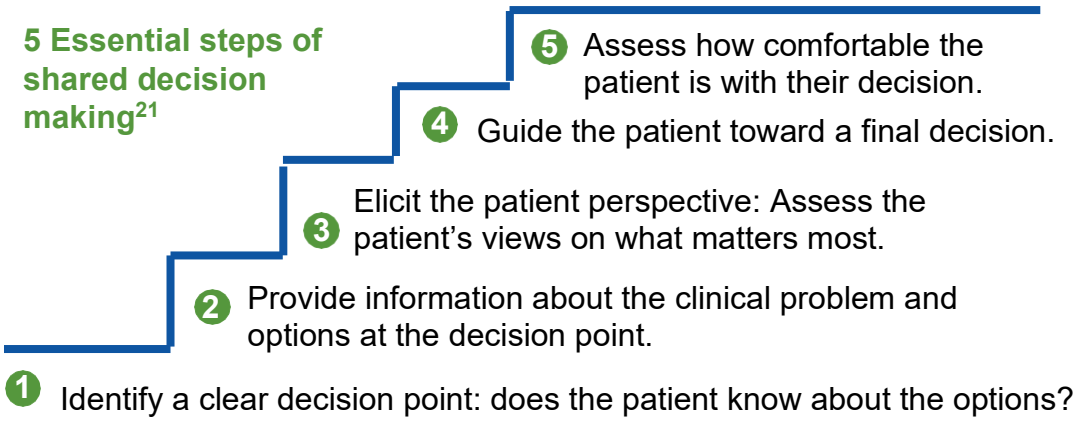
- Review of all relevant data from eligibility assessment
- Documentation of patient's understanding and informed consent-commitment/ willingness to treatment follow-up expectations (contraception, labs, alcohol, potential for corticosteroids post-gene therapy)
- Coordination of care between patient and HTC as well as referring and infusing centers when necessary
- Opportunity to meet with social worker or psychosocial support person at least once during the process
- Assess expectations before, during, and after gene therapy: acknowledging the burden of follow-up appointments associated with the treatment
- Ensure questions about family planning are addressed and understood. Barrier contraception is recommended for 2 years for males and their female partners of childbearing potential

Gene therapy discussion

The discussion between a healthcare provider (HCP) and a potential gene therapy patient is a key step in educating patients and addressing patient expectations, as well as assessing a patient's eligibility for the treatment.

The discussion can be initiated by either the patient who has an interest in gene therapy or an HCP who has identified a potentially appropriate patient for this option. As gene therapy is a novel therapeutic option that patients may be unfamiliar with, it is important for both patients and providers to be aligned in their understanding, expectations, and commitment to the process of gene therapy. Discussions regarding gene therapy should be tailored to each individual patient with hemophilia. There are several tools that can be used to facilitate discussions with patients, including the shared decision making (SDM) model.

The Canadian Task Force on Preventive Health Care (CTFPHC) has released an article regarding shared decision making in preventive health care. This five-step process for SDM includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient.[21]



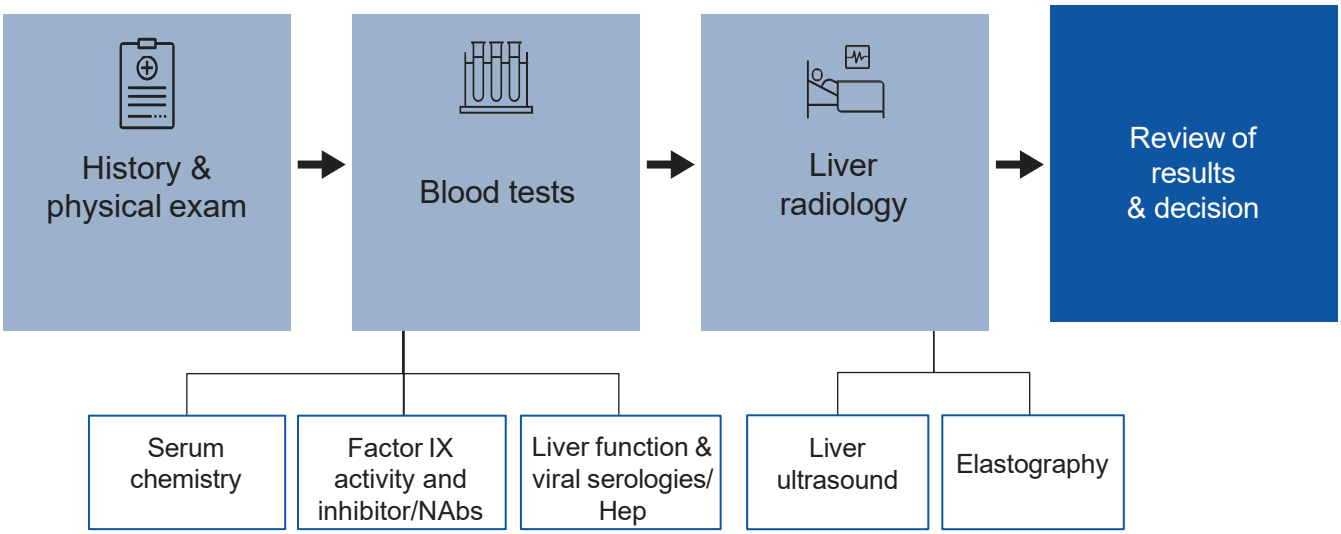
There are many other patient-friendly educational materials such as instructional videos and illustrated schematics available online. CSL Behring is developing a discussion guide that will be available through your local representative. Access the Canadian Hemophilia Society resources for gene therapy here: https://www.hemophilia.ca/gene-therapy/.

Example patient questions

- What is gene therapy and how does it work?
- How safe and effective is gene therapy? Will it cure my Hemophilia B?
- How long does it take for gene therapy to work? And for how long will it work?
- Will I still need Factor IX infusions?
- What are the risks and side effects?
- What's been the experience of other Hemophilia B patients in clinical trials?
- Am I a good candidate for gene therapy?
- Where will I go for the infusion and what's involved on the day of infusion?
- Where, how often, and how long will follow-up take place?
- Will I still be under the care of my HTC team?
- How will receiving gene therapy change my daily routine and lifestyle?
- Who will I contact if I need help?

Eligibility evaluation

A safe and appropriate gene therapy experience begins with the provider's assessment to make an informed decision about a potential patient's eligibility based on comprehensive review of results from the medical history, physical exam, and relevant laboratory and radiologic tests. This information, coupled with a holistic understanding of the patient's psychosocial history and current state will help to confirm the patient meets the criteria for what we know to be an appropriate candidate and competently understands and is committed to the process and lifestyle changes.



Key areas of evaluation that are further explained and particularly relevant to optimal gene therapy outcomes are hemophilia history and a thorough assessment of liver health.

Hemophilia history

A thorough Hemophilia B history not only validates a potential gene therapy patient's eligibility, but also provides an important baseline with which to compare and guide post-treatment clinical care, which may include:

- Frequency, type, and severity of bleeds
- Factor IX activity level
  - The use of different assays may impact the test results; therefore, use the same assay and reagents to monitor patients over time, if feasible
- Current Factor IX treatment regimen
- Factor IX-inhibitor titer test
  - In case of a positive test result for human Factor IX inhibitors, perform a re-test within approximately 2 weeks. If both the initial test and re-test results are positive, do not administer HEMGENIX to this patient
- Joint health status
- Psychosocial status

Immune-mediated neutralization of the AAV5 vector capsid

- In AAV-vector-based gene therapies, preexisting neutralizing anti-AAV antibodies (NAbs) may impede transgene expression at desired therapeutic levels. Following treatment with HEMGENIX, all subjects developed neutralizing anti-AAV antibodies
- For patient selection, baseline examination of AAV5-neutralizing antibodies is required. A patient blood sample is required for testing for AAV5-neutralizing antibodies. If a patient has AAV5-neutralizing antibodies above a pre-determined threshold they will not be eligible for treatment with HEMGENIX. If a patient has no detectable AAV5-neutralizing antibodies or neutralizing antibodies below the established threshold then the patient may be eligible for treatment with HEMGENIX
- CSL Behring, through Precision for Medicine, will make available the assay used in the HOPE-B clinical trial to identify pretreatment-neutralizing AAV5 antibodies

Liver health

- The liver performs vital functions including detoxification, production of bile for digestion and proteins such as relevant clotting factors, and storage of ADEK vitamins and carbohydrates for energy
- HEMGENIX delivers the Padua variant of the human Factor IX gene to hepatocytes, and functional delivery and incorporation of the Factor IX Padua variant into hepatic cells is the key to an optimal outcome
- Preexisting liver conditions can impact the need to intervene after gene therapy, therefore a healthy liver is necessary for durability of Factor IX expression and to help maintain long-term protein production
- At minimum, all gene therapy candidates require a liver health assessment consisting of liver enzyme tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin) as well as hepatic ultrasound and elastography. It is recommended that the ALT test is repeated at least once prior to HEMGENIX administration to establish patient's ALT baseline
- Clear guidelines and recommendations for the definition and management of preexisting liver disease in patients with hemophilia undergoing evaluation for gene therapy is lacking, necessitating collaboration with hepatologists and other disciplines throughout the process
- In case of radiological liver abnormalities and/or sustained liver enzyme elevations, consideration of a consultation with hepatologist is recommended to assess eligibility for HEMGENIX noting that patients with severe hepatic impairment or active liver infections were excluded from clinical studies with HEMGENIX

Measures of liver health

Medical history

- Alcohol consumption
- Diet and lifestyle choices
- Non-alcoholic fatty liver disease is the most common liver disease in Canada, affecting over 7 million people[22]
- Viral infections. Both viral hepatitis B (easily controlled but not curable) and hepatitis C (easily cured) can lead to advanced fibrosis with decompensated cirrhosis
- Medication, drugs (prescription, over-the-counter, or illicit) and supplements history

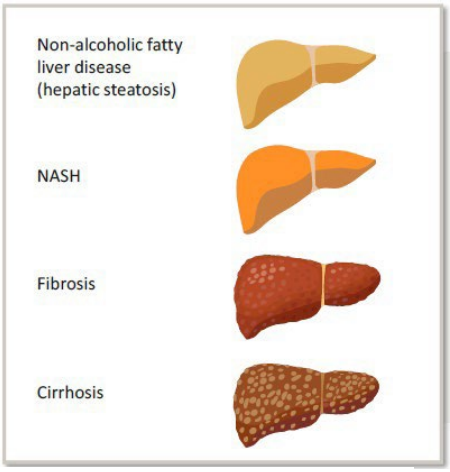
Liver enzyme and synthetic function tests (e.g., AST, ALT, albumin, International Normalized Ratio [INR])

- Elevated AST and ALT indicate liver inflammation and liver cell death
- Very insensitive markers for predicting extent of liver damage and may be normal in advanced fibrosis/cirrhosis

Despite limitations, it's important to document baseline levels and remove any confounding factors before initiating gene therapy.

Transient elastography (e.g., FibroScan)

- Used to measure liver stiffness and fibrosis
- Easily performed in the office and renders instant results but requires interpretation
- Measures speed of sound wave through liver, which is proportional to "stiffness," which is related to fibrosis
- Stiffness result is measured in kPa – normal results are usually 2-7 kPa
- Fibrosis score (F0-F4) is calculated using the stiffness result and medical history
- Patients with advanced fibrosis (3 or 4) are at risk for ascites, liver cancer, and esophageal varices



Luxon BA. Presentation at THSNA Symposium. 2022.[23]

Point shear wave elastography

- An ultrasound applied technique used to measure tissue stiffness as a result of a disease
- It can be used to evaluate liver stiffness as a result of liver cirrhosis and could correlate it with esophageal varices

Magnetic resonance elastography (MRE)

- A technology that combines magnetic resonance imaging with low-frequency vibrations to create a visual map (elastogram) that shows stiffness of body tissues
- Currently, MRE is used to detect stiffening of the liver caused by fibrosis and inflammation in chronic liver disease

Blood-based biomarkers

- Aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis score index (FIB-4) estimate the degree of fibrosis
- FibroTest provides a quantitative score to assess liver damage
- Non-alcoholic fatty liver disease fibrosis score is used to assess patients with non-alcoholic fatty liver disease (NAFLD) for fibrosis

These tests have a high degree of sensitivity and specificity to the degree of fibrosis; however, they are not used to assess inflammation.

Required liver tests for HEMGENIX

- ALT, AST, ALP, and total bilirubin
- Liver ultrasound and elastography

In case of radiological liver abnormalities and/or sustained liver enzyme elevations, consider a consultation with hepatologist to assess eligibility for HEMGENIX.

HEMGENIX patient eligibility considerations

- Adults (≥18 years) with Hemophilia B (congenital Factor IX deficiency)
- Currently receiving Factor IX replacement therapy for routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- No neutralizing Factor IX inhibitors as assessed by an initial test and re-test for positive results
  - In case of a positive test result for human Factor IX inhibitors, perform a re-test within approximately 2 weeks. If both the initial test and re-test results are positive, do not administer HEMGENIX to this patient
- No advanced hepatic impairment, including cirrhosis, advanced liver fibrosis, or uncontrolled (active) Hepatitis B and C (as demonstrated by radiological liver abnormalities), sustained liver enzymes, and/or viral serology results evaluated by a hepatologist and deemed exclusionary. Patients with elastography of ≥9 kPa or suggestive of or equal to METAVIR stage 3 disease were not studied
- No known severe infection or any other significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, cardiovascular, or alcoholism
- No allergy/anaphylaxis history to any components of HEMGENIX
- No previous gene therapy treatment
- Deemed able to provide informed consent and comply with rigors of the process
- HEMGENIX is not intended for administration in women

Sample evaluation worksheet

Patient identifier

Patient name: John Smith
Age: 23
Allergies: None

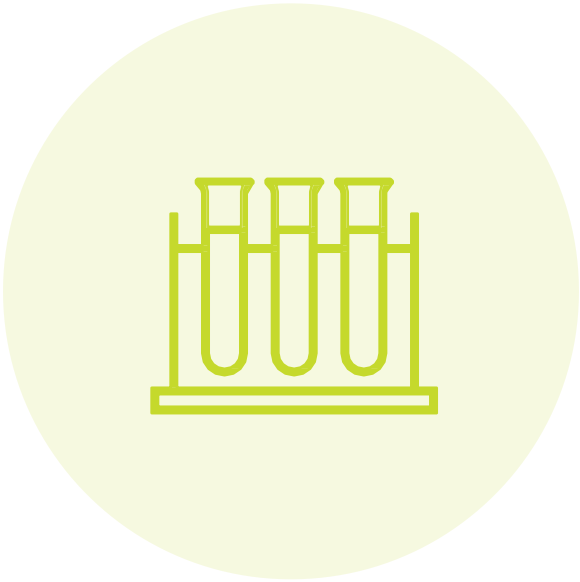
Hemophilia history Factor IX activity baseline level: 4% OSA ☑ CSA ☐ Current treatment: Alprolix Severe/moderate Hemophilia B ☑ Currently on Factor IX prophylaxis therapy ☑ No history of Factor IX inhibitors ☑ Historical life-threatening hemorrhage, or repeated, serious spontaneous bleeding episodes ☑ No previous gene therapy treatment ☑	**Date** 06/30/2024
Past medical history: N/A **Medication list** (incl. supplements/vitamins)**:** Vitamin D History of alcohol use: Yes ☐ No ☑ Pt Wt (within 30 days of infusion): 77 kg	**Date** 06/30/2024
Relevant lab results ALT: 19.0 mU/mL AST: 21.1 mU/mL Total bilirubin: 0.6 mg/dL ALP: 90 U/L Factor IX inhibitor titer: <0.6 BU	**Date** 06/30/2024
Radiology Liver ultrasound results: Normal Elastography results: Normal	**Date** 05/15/2024
Psychosocial factors Referral to Social Worker ☑ Understands the process of gene therapy ☑ Willingness to comply with rigorous follow-up and lifestyle modifications as necessary ☑ Ability to provide informed consent ☑ Commitment to follow-up ☑ Family planning ☑	**Date** 06/30/2024
Pre-administration education Gene therapy basics ☑ Product information ☑ Gene therapy process ☑	06/30/2024

Please see Appendix for worksheet

Decision

- The decision to proceed with gene therapy for a patient is made after **a full review of all relevant data obtained during the eligibility evaluation** and may involve multiple providers
- The decision-making process may also require multiple discussions between patients and HCPs, as well as between administration and referral centers after patient's referral
- As the decision is shared between patient and provider, there may be additional elements to consider aside from the diagnostic evaluation. These elements may include the patient's understanding of the process, compliance and adherence to the follow-up, and commitment to any lifestyle modifications that may be necessary
- Once the decision has been reached, it would be prudent to document the discussion and the patient's agreement. The form of documentation and responsible parties should be established by each institution

HEMGENIX Preparation and Administration



Introduction

The next step in the gene therapy clinical journey is the preparation and administration of the gene therapy and delivery to the patient. This section provides step-by-step guidance on the preparation and administration of HEMGENIX, as indicated in the Product Monograph, as well as a sample infusion day checklist, which is intended to outline the different providers that may be involved during this process and their respective preparations to ensure a safe outcome for the patient.

Of utmost importance is ensuring the patient has a clear understanding of the plan at discharge, including instructions for follow-up.

HEMGENIX storage and handling

Product storage

- HEMGENIX is shipped at 2°C to 8°C
- Cold chain storage and handling is required
- Upon receipt, vials should be stored in a refrigerator at 2°C to 8°C in the original carton, protected from light until time of dilution and administration
- Once diluted with 0.9% normal saline, HEMGENIX can be stored in the infusion bag protected from light at 15°C to 25°C after dose preparation
- The administration of HEMGENIX dose to the patient should be completed within 24 hours after the dose preparation
- HEMGENIX **should not be frozen**
- The shelf life of HEMGENIX is 24 months from the date of manufacture

Handling

General Instructions

- Follow universal biohazard precautions for handling and according to instructional policies or provincial regulations. For instructions on preparation, handling, measures to take in case of accidental exposure to and disposal of the medicinal product, see SPECIAL HANDLING INSTRUCTIONS in the Product Monograph
- HEMGENIX does not contain preservatives
- Use aseptic techniques during the preparation and administration of HEMGENIX. Use a new needle/vial adapter and syringe for each HEMGENIX vial
- DO NOT expose HEMGENIX to the light of an ultraviolet radiation disinfection lamp.
- Confirm that the patient’s identity matches with the patient-specific identifier number on the outer carton
- Verify the required dose of HEMGENIX 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
- Confirm that the carton contains sufficient number of vials to prepare the diluted HEMGENIX patient-specific infusion bag
- In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except for 0.9% normal saline solution used HEMGENIX dilution prior to administration. The compatibility of HEMGENIX was established for intravenous infusion lines with integrated in-line 0.2 µm filters made out of polyethersulfone (PES)
- After dilution, HEMGENIX should be a clear, colourless solution

HEMGENIX dose calculation

The recommended dose of HEMGENIX is 2×10^{13} genome copies per kilogram (kg) of body weight administered as an IV infusion after dilution with 0.9% sodium chloride solution (normal saline).

Example

For a patient with a body weight of 85 kg, dilute the 170 mL of HEMGENIX dose in **one** 500 mL 0.9% normal saline solution infusion bag.

For a patient with a body weight of 128 kg, dilute 256 mL of HEMGENIX dose in **two** 500 mL 0.9% normal saline solution infusion bags (128 mL in each bag).

Number of HEMGENIX vials needed = HEMGENIX dose (in mL) divided by 10 (round up to next whole number of vials). The division factor 10 represents the extractable volume of HEMGENIX from each vial (10 mL vials).

- **The total volume of the patient's HEMGENIX dose to be diluted may be less than the total volume of vials needed**

Patient weight	HEMGENIX dose (mL) (body weight multiplied by 2)	Number of vials needed (HEMGENIX dose [mL] divided by 10, then rounded up)
85 kg	170 mL	17
128 kg	256 mL	26

HEMGENIX preparation for administration: ancillary supplies

Required supplies and materials for product preparation

- Normal saline infusion bag(s)* of 500 mL (1 to 2 bags based on patient's body weight)
- Labels** for the infusion bag(s) of 500 mL
- IV Infusion line/drip chamber* primed with 0.9% normal saline
- Infusion bag connector(s)
- 20 mL or larger Luer-lock syringes*
- 20 G needles* or vial adaptors*
- 70% isopropyl alcohol
- Sharps disposal container
- Personal protective equipment: including gloves, safety goggles, protective clothing and masks. These should be worn while handling and administering HEMGENIX.

Component*	Material of construction
Normal saline infusion bag (0.9% normal saline)	PE/PP copolymer (PVC-free) (Stability after dilution was established using PE/PP copolymer, PVC-free infusion bags with 0.9% normal saline)
20 G needle	Stainless steel
Vial adapter	PP, Silicone; PP, stainless; MABS, acrylic silicone; ABS
Luer-lock syringe	PP, Silicone
Infusion line/drip chamber	PVC/TOTM, PP/styrene-ethylene-butylene-styrene

MABS = Methyl methacrylate acrylonitrile butadiene styrene; PE = Polyethylene; PP = Polypropylene; PVC = Polyvinyl chloride; TOTM = Trioctyltrimellitate; ABS = Acrylonitrile butadiene styrene

**Information to be included on the infusion bag label

- Product name: Diluted HEMGENIX
- Patient identifier
- Expiration date/time (24 h from the vial removal from refrigerator)
- Storage condition: Room temperature [15-25 °C] protected from light (ex. use of amber bag)
- Contains recombinant viral vector product
- Number of infusion bags (e.g., 1 of 2 bags / 2 of 2 bags, or 1 of 1 bag)

HEMGENIX preparation steps

Preparation

Step 1: Product preparation

HEMGENIX must be diluted with 0.9% normal saline solution prior to administration.

- Prior to dilution, gently swirl the vial 3 times (about 10 seconds) to homogenize the HEMGENIX suspension. To avoid foaming, DO NOT shake the HEMGENIX vial(s).
- Next, withdraw the volume of the calculated dose from the 500 mL infusion bag(s) of 0.9% normal saline solution, depending on patient's body weight.
    - For patients with a body weight of <120 kg, dilute the HEMGENIX dose in **ONE** 500 mL 0.9% normal saline solution infusion bag.
    - For patients with a body weight of ≥120 kg, dilute the HEMGENIX dose in **TWO** 500 mL 0.9% normal saline solution infusion bags, dividing the HEMGENIX dose equally between the two bags.

Patient body weight	Number of 500 mL 0.9% normal saline infusion bag(s) required	Volume of saline solution to withdraw
Less than 120 kg body weight	One	Equal to the total HEMGENIX dose (in mL) from one bag
Equal to or more than 120 kg body weight	Two	Equal to the total HEMGENIX dose (in mL). Remove half of the dose equivalent volume from each of the two bags

- Remove the amount of 0.9% normal saline with a luer lock syringe at the mixing adapter site of the applicable connector.

Step 2: Addition of HEMGENIX to the infusion bags

- 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.
- **DO NOT** add HEMGENIX into the airspace of the infusion bag during diluting.
- Gently invert the infusion bag(s) at least 3 times to mix the solution and ensure even distribution of the diluted product.
- 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.
- 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.
- 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.

HEMGENIX administration

Administer HEMGENIX as a single-dose intravenous infusion through a peripheral venous catheter

1. Visually inspect diluted HEMGENIX prior to administration. The diluted HEMGENIX should be clear and colourless
   - DO NOT use if particulates, cloudiness, or discoloration are visible
   - Use the product as soon as possible following dilution. **DO NOT** use the diluted HEMGENIX more than 24 hours after the dose preparation
2. Use an integrated (in-line) 0.2 µm filter made out of polyether sulfone (PES)
3. The diluted HEMGENIX solution must be administered into a peripheral vein by a separate intravenous infusion line through a peripheral venous catheter
4. Subsequently, connect the pre-filled IV infusion line/drip chamber to the main intravenous line which has been primed with sterile 0.9% normal saline solution prior to use
5. Infuse diluted HEMGENIX at a constant infusion rate of 500 mL/hour (8 mL/min)
   - DO NOT administer HEMGENIX as an intravenous push or bolus
   - DO NOT infuse the product faster than 500 mL/hour
   - DO NOT infuse the diluted HEMGENIX solution in the same intravenous line with any other products
   - DO NOT use a central line or port
6. After the entire content of the bag(s) is infused, flush the IV infusion line/drip chamber at the same infusion rate with 0.9% normal saline solution to ensure all HEMGENIX is delivered
   - Treat spills of HEMGENIX with a virucidal agent with proven activity against non-enveloped viruses
   - Dispose of unused product and disposable materials that may have come in contact with HEMGENIX in accordance with local biosafety guidelines applicable for handling and disposal of pharmaceutical waste

In the event of an infusion reaction during administration

- Symptoms of an infusion-related reaction may include chest tightness, headaches, abdominal pain, light-headedness, flu-like symptoms, shivering, flushing, rash, and hypertension
- Closely monitor patients for signs or symptoms of an infusion reaction throughout the infusion period and for at least 3 hours after end of infusion
- The rate of infusion may be reduced or stopped, to manage the infusion reaction
  - If the infusion is stopped, restart at a slower rate when the infusion reaction is resolved and based on patient tolerability
- If the infusion rate needs to be reduced, or stopped and restarted, HEMGENIX should be infused within 24 hours after the dose preparation
- Consider treatment with a corticosteroid or antihistamine for management of an infusion reaction
- In clinical studies with HEMGENIX in adult patients, three individuals had their infusions temporarily interrupted and resumed at a slower infusion rate. One individual who had their infusion stopped due to a serious hypersensitivity reaction did not resume treatment and had no measurable response to therapy

HEMGENIX administration: ancillary supplies

Required supplies and materials

- Winged intravenous needle* or catheter set*
- Infusion pump
- 0.2 µm in-line filter*
- Antiseptic skin preps
- 70% isopropyl alcohol wipes
- Gauze and tape, or transparent dressing
- Sharps disposal container
- Virucidal agent to treat spill/spill kit
- Personal protective equipment, including gloves, safety goggles, protective clothing and masks

Component*	Material of construction
Winged IV needle or catheter set	PVC/TOTM, MABS
0.2 µm in-line filter	PES
Catheter	PVC/DEHT, Stainless steel

DEHT = di(2-ethylhexyl)terephthalate; MABS = methyl methacrylate acrylonitrile butadiene styrene; PES = polyether sulfone; PVC = polyvinyl chloride; TOTM = trioctyltrimellitate

Discharge

- Patient may leave the clinic after all post-infusion assessments have been performed
- Patients should receive a medical letter explaining they underwent gene therapy
- Patients should receive detailed instructions on signs and symptoms to report in the immediate post-infusion period and their follow-up schedule of labs and visits, as well as relevant contact information in case of emergencies. It may also be helpful for patients to receive a treatment card prior to discharge documenting details about the infusion day

Disposal

- HEMGENIX is a recombinant adeno-associated virus. Unused medicinal product and all materials (solid and liquid waste) that have been in contact with the recombinant viral vector product should be handled and disposed of as potentially infectious waste in a container dedicated to biohazard material, autoclaved and destroyed in accordance with local biosafety guidelines
- Non-disposable materials should be cleaned with a disinfectant with proven virucidal activity for non-enveloped viruses 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

Sample infusion day checklist

Patient identifier

Patient name: John Smith

Age: 23

Allergies: None

	Date/Time
Infusion suite preparation Administration supplies in place: Pump or equivalent programmable pole mount ☑ Peripheral IV (PIV) start supplies/saline flushes available ☑ Emergency supplies available: Epinephrine ☑ Antihistamine ☑ Corticosteroids ☑ Code cart ☑	07/08/24 8:05
Admission Patient present at site ☑ Informed consent complete ☑ Intake complete ☑ Baseline vitals ☑ Weight verified ☑ Labs complete: Liver function tests ☑ Metabolic panel ☑ Importance of maintaining a healthy liver, specifically as it relates to lifestyle modifications (alcohol consumption, liver-toxic medications, etc.) reviewed ☑ Adherence to follow-up in the first 12 weeks is critical ☑	07/08/24 7:45
Pharmacy preparation • Pharmacy to prepare diluted HEMGENIX IV bag(s) ☑ • Supplies for drug infusion from pharmacy: premixed-primed tubing/filter ☑ • Saline flush bag needed post-infusion (0.9% normal saline for flush) ☑	07/08/24 8:10
Administration • 2 IV sites should be established in the event of allergic reaction or should the existing IV go interstitial ☑ • Monitor the site every 5 minutes ☑ • Before drug is administered two HCPs should check that the IV is patent and intact ☑ • Vital signs upon initiation of infusion and throughout infusion period ☑ • HEMGENIX should not be infused in the same IV line with any products other than the 0.9% saline ☑ • Begin administration at a constant infusion rate of 500 mL/hour (may be reduced to 250 mL/hour as needed/patient) ☑ • Flush the IV infusion line/drip chamber at the same infusion rate with 0.9% normal saline solution to ensure all HEMGENIX is delivered ☑ Detailed information on how to manage reactions including: • Restart process • Infusion reaction adverse event and actions	Started at 8:15 Ended at 9:16
Discharge Patient monitored during and at least 3 hours after administration ☑ Patient discharge instructions: • Signs and symptoms to report to infusing team physician/nurse coordinator ☑ • Post-treatment follow-up schedule of labs, diagnostics, and exams ☑ • Patient is provided a medical letter stating they underwent gene therapy ☑ • Coordinate with patient's home pharmacy: Prescribe a corticosteroid and provide prescription and discharge note with pharmacy ☑	Monitored until 12:27 at discharge

Please see Appendix for worksheet

Post-Treatment Monitoring

Introduction

This step in the journey, post-treatment monitoring and management, is one that sets the foundation for understanding the safety and efficacy of HEMGENIX and guides future care decisions. After infusion of HEMGENIX, there is a critical period where follow-up visits and lab work may be more frequent, specifically assessing LFTs and Factor IX activity levels. This is necessary to evaluate the response to the gene therapy as well as potential immune-mediated hepatotoxicity, which may need immediate attention and intervention. Additional testing may be required and will be based on provider discretion. The ultimate schedule of testing should be determined and tailored, if necessary, by the treating physician and communicated clearly with the patient.

Liver function

- IV administration of a liver-directed AAV vector, like HEMGENIX, could potentially induce a cellular immune response to the capsid once it is transduced into the hepatocytes, manifesting as asymptomatic transaminitis, with the potential for compromised or loss of Factor IX transgene expression.[24,25] In clinical studies with HEMGENIX, transient, asymptomatic, and predominantly mild elevations in transaminases were observed, occurring most often in the first 4 months after administration, and resolved either spontaneously or with administration of a corticosteroid
- Perform regular liver enzyme testing to monitor for liver enzyme elevations, which may indicate immune-mediated hepatotoxicity
  - Monitor ALT and AST (transaminase) levels by testing weekly for 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. Continue to monitor transaminases in all patients who developed liver enzyme elevations until liver enzymes return to baseline
  - In the event of ALT increase to above normal limits or to twice the patient's baseline in the first 3 months post-dose, consider implementing a course of corticosteroids. For patients with clinically relevant ALT increases who need corticosteroid treatment, administer the recommended starting dose of 60 mg/day of oral prednisolone or prednisone, with a subsequent taper in response to normalization of the ALT levels

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

[$] 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.

- In the clinical studies, the mean duration of corticosteroid use for elevated transaminases was 81.4 days (standard deviation [SD] 28.6) and ranged from 51 to 130 days
- Perform regular alpha-fetoprotein (AFP) level testing and abdominal ultrasound (e.g., annually) in patients with preexisting risk factors for hepatocellular carcinoma

Factor IX activity

- The assessment of Factor IX activity level is a direct measure of the response to gene therapy
- Factor IX activity (e.g., weekly for at least 3 months)
- Monitor patients regularly for their Factor IX activity
- Use of exogenous Factor IX concentrates before and after HEMGENIX administration may affect an accurate estimation of HEMGENIX-derived Factor IX activity.
  - The use of different assays may impact the test results; therefore, use the same assay and reagents to monitor patients over time, if feasible
- It is critically important that the patient understands and maintains close communication with the care team about all clinical symptoms (e.g., bleeds, pain, changes in physical function, activity level) as well as other new medical conditions or the need for surgery
- Discontinuation of continuous routine prophylaxis with exogenous human Factor IX
  It may take several weeks before improved hemostatic control becomes apparent after HEMGENIX infusion (for more detailed information see Product Monograph - Pharmacokinetics 10.3). Therefore, continued hemostatic 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 (e.g., weekly for at least 3 months) is recommended post-dose to follow patient's response to HEMGENIX

Factor IX inhibitors

- 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.

Vector biodistribution and shedding

- Vector distribution in blood, and vector shedding in semen and other excreta and secreta can occur post-infusion. It is not known how long this will continue. Patients should not donate blood, organs, tissues, or cells for transplantation
- Shedding and Contraception:
  Shedding of HEMGENIX vector DNA will occur in blood, feces and semen of patients receiving HEMGENIX. Since some patients have detectable viral/transgene DNA detected in semen between 1 to 2 years following administration of HEMGENIX, barrier contraception is recommended for 2 years for males and their female partners of childbearing potential (for more detailed information see Product Monograph-Pharmacokinetics 10.3 Vector DNA shedding)

Monitoring post-infusion

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 7 WARNINGS AND PRECAUTIONS in the Product Monograph). 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).
    - Monitor patients regularly for their Factor IX activity (see 7 WARNINGS and PRECAUTIONS, Monitoring and Laboratory Tests in the Product Monograph).
    - Use of exogenous Factor IX concentrates before and after HEMGENIX administration may affect an accurate estimation of HEMGENIX-derived Factor IX activity.
- Perform regular alpha-fetoprotein (AFP) level testing and abdominal ultrasound (e.g. annually) in patients with preexisting risk factors for hepatocellular carcinoma (See 7 WARNINGS AND PRECAUTIONS in the Product Monograph).
- 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.

Example schedule of laboratory tests

Short-term post-treatment monitoring per HEMGENIX prescribing information		
Test	**Month 1-3**	**Month 4-12**
Factor IX activity	Weekly	HCP discretion
Factor IX inhibitor testing (if bleeding is not controlled or Factor IX levels decrease)	HCP discretion	HCP discretion
Liver enzyme tests (including transaminases)	Weekly	HCP discretion
AFP levels and abdominal ultrasound (in patients with risk factors for hepatocellular carcinoma)		Regularly (annually)

Sample calendar

Sun	Mon	Tues	Wed	Thurs	Fri	Sat
	1/1 Admin Day	1/2	1/3	1/4	1/5	1/6
1/7	1/8 Week 1 Lab Check	1/9	1/10	1/11	1/12	1/13
1/14	1/15 Week 2 Lab Check	1/16	1/17	1/18	1/19	1/20
1/21	1/22 Week 3 Lab Check	1/23	1/24	1/25	1/26	1/27
1/28	1/29 Week 4 Lab Check	1/30	1/31			

Please see Appendix for worksheet

Communication and coordination

In the case where the patient's infusing site and referral center are different, it will be important to coordinate the care between the two to ensure appropriate transition of patient care in this critical period. As such, providers should consider the following:

- Establishing a communication plan between the infusing site and referral center wherein the responsibilities of the respective providers such as monitoring of labs and providing timely guidance on an intervention are clearly documented
- It will be important to establish a communication plan with the patient to understand their post-treatment plan, including but not limited to:
  - Where they will receive their post-treatment care
  - Where labs will be drawn
  - A method by which results will be communicated
  - Emergency contact information

Long-Term Monitoring and Management

Introduction

Over time, as the response to gene therapy is established, the frequency of testing may decrease and mirror a similar cadence of follow-up as a patient's past hemophilia care, prior to gene therapy. As is the case through the clinical journey, maintaining an open line of communication over the long term is essential to understanding an individual patient's journey and maintaining optimal hemophilia care. The following are some elements to consider as patients are monitored over time:

- Maintaining a line of communication between patient and healthcare provider with an understanding of the follow-up schedule as well as situations where patients may need more immediate evaluation, including but not limited to, surgery, bleeding, and trauma
- Patients with preexisting risk factors for hepatocellular carcinoma will need regular AFP testing and abdominal ultrasound screenings in the 5 years following administration
- Continued data collection and entry into the CBDR registry will help the community understand the long-term safety and efficacy of HEMGENIX
- As gene therapy is a novel therapeutic option, a multidisciplinary and collaborative approach to patient is crucial to ensure an optimal outcome

Long-term data collection

- Canadian Bleeding Disorder Registry (CBDR) will be linked with the WFH registry
- The World Federation of Hemophilia is developing a global gene therapy registry to provide robust surveillance of safety and efficacy of gene therapy for people with hemophilia who received treatment by clinical trial or commercial product[25]

Appendix

Glossary of terms

AAV, adeno-associated virus

AAV5, adeno-associated viral vector of serotype 5

ABS, acrylonitrile butadiene styrene

AHRQ, Agency for Healthcare Research and Quality

AFP, alpha-fetoprotein

ALP, alkaline phosphatase

ALT, alanine aminotransferase

APRI, aspartate aminotransferase-to-platelet ratio index

AST, aspartate aminotransferase

ATHN, American Thrombosis & Hemostasis Network

CBDR, Canadian Bleeding Disorder Registry

cDNA, complementary DNA

CSA, chromogenic substrate assay

CSTD, closed system transfer device

DEHT, di(2-ethylhexyl)terephthalate

FDA, Food and Drug Administration

FIB-4, fibrosis score index

G, gauge

gc, genome copies

GTPO, gene therapy process operationalization

HC, Health Canada

HCP, healthcare provider

HTC, Hemophilia Treatment Center

INR, International Normalized Ratio

IV, intravenous

LFT, liver function test

LP1, liver-specific promoter 1

MABS, methyl methacrylate acrylonitrile butadiene styrene

METAVIR, meta-analysis of histological data in viral hepatitis liver fibrosis scoring system

MRE, magnetic resonance elastography

NAb, neutralizing antibody

NAFLD, non-alcoholic fatty liver disease

NAPRA, National Association of Pharmacy Regulatory Authorities

NASH, nonalcoholic steatohepatitis

NBDF, National Bleeding Disorders Foundation

OSA, one-stage assay

PE, polyethylene

PES, polyether sulfone

PIV, peripheral intravenous

PP, polypropylene

PVC, polyvinyl chloride

SD, standard deviation

SDM, shared decision making model

TOTM, trioctyltrimellitate

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Evaluation checklist

Patient identifier

Patient name:
Age:
Allergies:

Hemophilia history Factor IX activity baseline level: _____ OSA ☐ CSA ☐ Current treatment: _____ Severe/moderate Hemophilia B ☐ Currently on Factor IX prophylaxis therapy ☐ No history of Factor IX inhibitors ☐ Historical life-threatening hemorrhage, or repeated, serious spontaneous bleeding episodes ☐ No previous gene therapy treatment ☐	**Date**
Past medical history: _____ **Medication list (**incl. supplements/vitamins**):** _____ History of alcohol use: Yes ☐ No ☐ Pt Wt (within 30 days of infusion): _____	**Date**
Relevant lab results ALT: _____ AST: _____ Total bilirubin: _____ ALP: _____ Factor IX inhibitor titer: _____	**Date**
Radiology Liver ultrasound results: _____ Elastography results: _____	**Date**
Psychosocial factors Referral to Social Worker ☐ Understands the process of gene therapy ☐ Willingness to comply with rigorous follow-up and lifestyle modifications as necessary ☐ Ability to provide informed consent ☐ Commitment to follow up ☐ Family planning ☐	**Date**
Pre-administration education Gene therapy basics ☐ Product information ☐ Gene therapy process ☐	**Date**

Infusion day checklist

Patient identifier

Patient name:
Age:
Allergies:

Infusion suite preparation	**Date/Time**
Administration supplies in place: Pump or equivalent programmable pole mount ☐ Peripheral IV (PIV) start supplies/saline flushes available ☐ Emergency supplies available: Epinephrine ☐ Antihistamine ☐ Corticosteroids ☐ Code cart ☐	
Admission Patient present at site ☐ Informed consent complete ☐ Intake complete ☐ Baseline vitals ☐ Weight verified ☐ Labs complete: Liver function tests ☐ Metabolic panel ☐ Importance of maintaining a healthy liver, specifically as it relates to lifestyle modifications (alcohol consumption, liver-toxic medications, etc.) reviewed ☐ Adherence to follow-up in the first 12 weeks is critical ☐	
Pharmacy preparation • Pharmacy to prepare diluted HEMGENIX IV bag(s) □ • Supplies for drug infusion from pharmacy: premixed-primed tubing/filter ☐ • Saline flush bag needed post-infusion (25-50 mL bag) ☐	
Administration • Vital signs upon initiation of infusion and throughout infusion period ☐ • HEMGENIX should not be infused in the same IV line with any products other than the 0.9% saline ☐ • Begin administration at a constant infusion rate of 500 mL/hour (may be reduced to 250 mL/hour as needed/patient) ☐ • Flush the IV infusion line/drip chamber at the same infusion rate with 0.9% normal saline solution to ensure all HEMGENIX is delivered ☐	
Discharge Patient monitored during and at least 3 hours after administration ☐ Patient discharge instructions: • Signs and symptoms to report to infusing team physician/nurse coordinator ☐ • Post-treatment follow-up schedule of labs, diagnostics, and exams ☐ • Prescription for oral corticosteroids (for expedient response should transaminitis occur) ☐	

Post-treatment monitoring and management calendar

Sun	Mon	Tues	Wed	Thurs	Fri	Sat

National Bleeding Disorders Foundation Gene Therapy Psychosocial Assessment Template

To access the most up-to-date version of the Gene Therapy Psychosocial Assessment Template, please visit https://www.bleeding.org/sites/default/files/document/files/Gene-Therapy-Psychosocial-Template-MASAC-Reviewed.pdf

For additional information, please visit https://www.bleeding.org/healthcare-professionals/allied-healthcare/social-work

Important contact information

For Customer Service Inquiries
For Customer service inquiries during business hours 613-232-2386
For urgent inquiries and afterhours service 514-219-7560

For Healthcare Providers/Medical Professional Inquiries
For Healthcare Providers/Medical Professionals who are interested in product information, education and support materials, please visit us at hcp.cslbehring.ca

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at AdverseReporting@CSLBehring.com and visit Health Canada's website on Adverse Reaction Reporting (canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or calling toll-free at 1-866-234-2345.

Adverse Drug Reactions (ADRs)
If you want to report an adverse reaction with any of our products, contact us at: 1-514-219-7560 (24-hour number) or AdverseReporting@cslbehring.com