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# HEMGENIX
# GENE-THERAPY FOR HEMOPHILIA B

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# ABBREVIATIONS

| | |
|---|---|
| AAV | adeno-associated virus |
| AAV5 | adeno-associated virus serotype 5 |
| ABR | annualized bleeding rate |
| AEs | adverse events |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| BU | Bethesda unit |
| CI | confidence interval |
| FIX | blood clotting factor IX |
| GAS-STH | German, Austrian, and Swiss Society for Thrombosis and Haemostasis |
| GT | gene therapy |
| HB | hemophilia B |
| HRQoL | health related quality of life |
| IC | International Consensus |
| ICER | Institute for Clinical and Economic Review |
| IU | international units |
| IV | intravenous |
| WFH | World Federation of Hemophilia |

# 1.0 INTRODUCTION

Hemophilia B is a rare, congenital, lifelong bleeding disorder characterized by a deficiency of blood clotting factor IX (FIX). Severe deficiency of FIX impairs the normal blood coagulation process, causing excessive bleeding upon trauma or surgery, and frequent spontaneous internal bleeds into joints. Not only are internal bleeds acutely painful, recurrent joint bleeds cause arthropathy, chronic pain, lifelong disability, and decreased quality of life. Additionally, people with a severe hemophilia B phenotype can experience neurological damage and life-threatening bleeds into vital organs.[1]

Prior to US approval of the novel gene therapy (GT; etranacogene dezaparvovec-drlb [Hemgenix]) for hemophilia B in November 2022, severe hemophilia B has been managed using intravenous (IV) replacement FIX products for prophylactic and acute treatment of bleeds.[1] GT for hemophilia aspires to cure the disease by providing healthy genes for the body to continually express adequate factor activity levels long-term.

Effective GT could help circumvent the burdens and complications inherent with prophylactic replacement factor therapy, related to IV access issues and sequelae from residual un-prevented bleeds. Prophylactic replacement factor regimens are demanding, requiring IV administration once or twice weekly with standard half-life FIX replacement products, or once every 10 to 14 days with extended half-life products.[1-4] Additionally, delivery of factor products can be complicated by infections of infusion ports, thrombosis related to intravenous delivery, and although rare, the development of neutralizing antibodies (ie, inhibitors) to the replacement FIX product. Inhibitor development is a serious complication that can render the patient's usual FIX product/dose ineffective.[1,5-7]

This report will review the place in therapy, efficacy, and safety of etranacogene dezaparvovec-drlb and will provide potential points for prior authorization development. Etranacogene dezaparvovec-drlb will be referred to as etranacogene throughout the report for simplicity. Etranacogene is provided as a one-time dose, approved only for adults with hemophilia B. Candidates are patients who are either receiving FIX prophylaxis, have a current or past history of life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes. Furthermore, patients must also (1) test negative for FIX inhibitors and (2) must either demonstrate normal liver laboratory/imaging assessment results or, in the case of liver abnormalities, be determined a candidate by a hepatologist. **Table 1** summarizes the dosage form, labeled indication, and dosing recommendations for this first-in-class GT for hemophilia B.

*Table 1. Etranacogene (Hemgenix) Indication and Dosing[8]*

| Dosage Form | Labeled Indication, Dosing, and Candidacy Determination |
|---|---|
| **Hemgenix** (etranacogene dezaparvovec-drlb)<br><br>*Intravenous infusion suspension*<br><br>Provided as a customizable kit for patient's weight, with 10 to 48 single-use vials ($1 \times 10^{13}$ gc/mL) and 10 mL extractable per vial | **Indicated for** adults with Hemophilia B (congenital factor IX deficiency) who:<br>1. currently use factor IX prophylactic therapy, **or**<br>2. have current or past history of life-threatening hemorrhage, **or**<br>3. have repeated, serious spontaneous bleeding episodes<br>**Recommended dose**: 2 x $10^{13}$ gc/kg body weight (or 2 mL/kg body weight)<br>• dose (in mL) = patient body weight (kg) x 2; infused no faster than 8 mL/min; dose should be used within 24 hours of preparation<br>• number of vials needed = dose (in mL) divided by 10 (round up to next whole number of vials)<br>**Before dose administration (ie, to determine candidacy), perform the following:**<br>• Factor IX inhibitor titer test: re-test cases with initial positive result within about 2 weeks. If both results are positive, the patient is not a candidate for etranacogene.<br>• Liver health assessment prior to dosing including ALP, ALT, AST, total bilirubin, hepatic ultrasound, and elastography. If there are radiological liver abnormalities and/or sustained liver enzyme elevations, consider consultation with a hepatologist to assess eligibility, and consider labeled warnings/precautions. |

*Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; gc, genome copies*

## 2.0 METHODS

During May 2023, the following websites were searched for clinical guidelines that address the treatment of hemophilia B with gene therapy:

- The National Hemophilia Foundation's Medical and Scientific Advisory Council: https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents
- World Federation of Hemophilia (WFH): https://elearning.wfh.org/resource/treatment-guidelines/
- American Society of Hematology: https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines
- United Kingdom Haemophilia Centre Doctors' Organisation: https://haemophilia.org.uk/resources/guidelines/
- Nordic Hemophilia Council: https://www.nordhemophilia.org/frontpage/guidelines
- Australian Haemophilia Centre Directors' Organisation: https://www.ahcdo.org.au/guidelines/national-guidelines
- The Trip database: https://www.tripdatabase.com/Home

A supplemental search for guidelines was performed in Ovid Medline (2015 through April 2023) for clinical guidelines. Upon identifying key clinical guidelines for hemophilia by the WFH (2018), a more targeted supplemental search for guidelines addressing etranacogene therapy, considering its approval date, was performed in Embase (2021 to May 25, 2023). A targeted literature search for additional information related specifically to etranacogene (eg, reviews, conference abstracts, guidelines) was performed in Ovid-Medline and Embase using key words and controlled vocabulary for the drug and hemophilia B (see search strategies under *Additional Evidence Search* in Appendix A). Other information

included in the report is from references cited by guidelines, reviews, ClinicalTrials.gov, and from the product prescribing information. The most recent professional prescribing information (ie, package insert) for etranacogene was obtained from the drug sponsor's website dedicated to the product. Google translator was used to translate the full-text of non-English publications (eg, the 2022 recommendations by the German, Austrian, and Swiss Society for Thrombosis and Haemostasis, a publication available in German[9]).

# 3.0 DISEASE OVERVIEW: HEMOPHILIA B

Hemophilia A (a deficiency of factor VIII) and hemophilia B (a deficiency of FIX) are the most common forms of hemophilia, with hemophilia A occurring in approximately 4 times as many persons as hemophilia B. Congenital hemophilia A and B result from genetic mutations on the X chromosome causing certain clotting factors to be absent or dysfunctional to various degrees.[10] Because males have one X chromosome, and therefore 1 copy of genes encoding certain clotting factors such as FIX, hemophilia occurs primarily in males. Although rarer, females may also have hemophilia, in which case both X chromosomes are affected (with mutated, missing, or inactive genes). It is estimated that only 3% of hemophilia B cases are in females.[11] Females may also be asymptomatic genetic carriers of hemophilia passing one defective clotting-factor gene to their child. The incidence of hemophilia (A and B altogether) is about 1 out of every 5,000 US male births. Based on data from 2012 through 2018, the US male prevalence of hemophilia overall (A and B) was estimated to be 33,000.[12] The estimated prevalence of hemophilia B of any severity is 3.8 cases per 100,000 males, with severe hemophilia B estimated at 1.1 cases per 100,000 males.[10,13]

Bleeding episodes in hemophilia patients can be spontaneous or triggered by trauma or surgery.[1] Recurrent, spontaneous bleeding into joints or muscle is typically more common with severe disease, occurring on a monthly basis in patients with severe disease untreated by prophylaxis.[1,7] Joints most often affected include the ankles, knees, and elbows.[14] Quality of life is diminished as long-term effects of recurrent bleeds manifest as synovitis, chronic joint disease, decreased range of motion, chronic pain, and disability.[1,15-17] Disease progression can lead to the need for radiosynovectomy, joint fusion, or joint replacement.[1,16] In addition to arthropathy, other complications of hemophilia may include seizures and paralysis if bleeding occurs in the brain, or death in the event of unstoppable bleeding or bleeding into a vital organ.[10,18] Patients with hemophilia express that their hemophilic condition can restrict educational, career, and recreational choices/opportunities, along with decisions regarding where to live and family structure.[7]

Even with the stand-of-care (ie, prophylactic replacement factor therapy), patients may still experience residual bleeds. Based on data from a US cohort between 2017 and 2019, the mean annual bleed rate for adults with severe hemophilia B on prophylactic FIX treatment and no history of inhibitors was 1.73 (standard deviation, 1.39), and about 9% experienced a bleed-related hospitalization during the 1-year period.[15]

## 3.1 Diagnosis

The diagnosis of hemophilia is prompted by observation of clinical features of hemophilia, laboratory assessment of clotting parameters (eg, prothrombin time, activated partial thromboplastin time [aPTT], and platelet function), and assessment of clotting factor activity levels to identify the potential cause of

bleeding. In patients with hemophilia A or B, prothrombin time and platelet counts are typically normal and aPTT is prolonged. However, this pattern can also be observed in other types of bleeding disorders (eg, deficiencies of factor XI or XII, or kininogen-related). Upon clinical suspicion of hemophilia B, the World Federation of Hemophilia (WFH) recommends using a **one-stage FIX assay** in the initial diagnostic workup, while taking into consideration that other clotting component deficiencies can influence results of this test. Since the laboratory assay is affected by many variables, WFH guidance addresses how to conduct the assay (see Chapter 3 of the WFH guidelines for full information).[1] **Genotype analysis** is also recommended to be offered to all people with hemophilia in order to determine the underlying variant(s) responsible for the disease and to help establish the diagnosis in mild hemophilic cases or elusive clinical presentations.[1]

In patients with hemophilia, the following clinical definition is used to define/identify an internal joint bleed: an unusual sensation 'aura' in the joint, plus at least one of the following[19]:

- increased swelling or warmth of the skin over the joint
- increased pain
    - Note that patients typically experience rapid resolution of acute pain following administration of replacement factors.
- progressive loss of range of motion or difficulty in using the limb compared to baseline

## 3.2 Disease Severity

**Table 2** describes the general classification of hemophilia severity based on factor activity level, according to the Factor VIII and IX Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haematosis. Factor activity levels are usually associated with a general bleeding phenotype; however, phenotypes are heterogeneous with respect to factor activity level, especially among patients with severe hemophilia and when comparing hemophilia A- and B-type patients.[1,14,19] As many as two-thirds of patients with hemophilia B are thought to have moderate to severe disease.[20]

*Table 2. Hemophilia Severity Classification and General Bleeding Profile[1,21]*

| Severity Classification Based on Factor Activity Level | | General Bleeding Profile Characterization |
|---|---|---|
| **Mild** | 5 to <40% of normal (5-40 IU/dL) | May experience excessive bleeding with trauma or surgery; spontaneous bleeds are unusual |
| **Moderate** | 1 to <5% of normal (1-5 IU/dL) | Excessive bleeding following minor trauma/surgery and occasionally spontaneously |
| **Severe** | <1% of normal (<1 IU/dL) | Frequent spontaneous bleeds and excessive bleeding following minor trauma/surgery |

# 4.0 MANAGEMENT OF HEMOPHILIA B

## 4.1 Standard-of-Care Treatment

Patients with symptomatic hemophilia are managed with replacement factor products to raise levels of the deficient factor. Depending on the patient's disease severity, the approach for factor replacement is either sole reliance on episodic therapy (ie, replacement factor given for acute bleeds), or prophylactic therapy (in addition to on-demand treatment for residual bleeds[22] if needed) to prevent spontaneous and trauma-induced bleeds. Prophylaxis has the ability to convert patients with more severe disease to a milder or nonhemophilic phenotype, providing superior benefits for hemophilic-related chronic disease outcomes compared to episodic therapy.[23,24] The WFH, which authors clinical treatment guidelines, describes that while episodic therapy is imperative for resolving pain, debilitation, and life-threatening scenarios of acute bleeds, it does not significantly modify the patient's bleeding profile (eg, frequency) nor the natural course of the disease, including progression of musculoskeletal damage and other complications.[1] In particular, **prophylactic therapy is the supported standard of care for severe hemophilia B and non-severe hemophilia B with a severe phenotype (ie, moderate hemophilia per factor activity level but with a severe bleeding phenotype)** in order to prevent bleeds and associated long-term sequela (as recommended by the 2022 International Consensus and by the 2020 WFH guideline for the management of hemophilia B; strong recommendation by the WFH).[1,25,26]

Dosing of prophylactic replacement factor is targeted to individualized goals for the FIX trough level, taking into account the patient's bleeding frequency, disease severity, lifestyle, peak activity level, clinical response, and ability to intensify the regimen. The minimum target level is typically a trough of >1 IU/dL (1%), but because patients may still remain at risk of bleeding between 1 and 5 IU/dL (1-5%), the target trough level may be set higher (>3-5%, or higher).[1,11] Nonetheless, target trough levels are described as an oversimplified treatment goal for prophylactic therapy.[25] Moreover, targets have largely been based on clinical significance demonstrated in hemophilia A, with less evidence available in hemophilia B[25]

Replacement factor therapy must be administered intravenously after reconstitution by patients and/or their caregivers. Patients and/or caregivers must learn aseptic administration techniques to allow for at-home infusion of their replacement product. The frequency of administration and the IV route of administration confer considerable treatment burden, particularly in children and given the use of standard half-life products which typically require **twice weekly** administration in order to maintain adequate FIX activity levels.[25] Extended half-life FIX products[*] are typically administered once **every 7-14 days** and may help decrease the treatment burden and improve adherence and outcomes. Prophylaxis with extended half-life FIX products can provide FIX activity levels >10 IU/dL (10%) for the majority of the dosing interval.[1] However, even with prophylactic therapy and the use of extended half-life products, patients may still experience residual and subclinical bleeds and joint damage. Patients can also develop persisting neutralizing antibodies (ie, inhibitors) against their replacement factor product; this occurs in approximately 3-5% of FIX-treated patients with hemophilia B, but may be higher (eg, 9%) in patients with severe disease.[1,5-7,11] Inhibitors can induce anaphylaxis or severe allergic reactions, and

[*] Four FIX replacement factor products are approved for prophylaxis therapy (Rixubis, Rebinyn, Alprolix, and Idelvion), and 3 of these are extended half–life products (Alprolix, Rebinyn, and Idelvion).

in some cases, nephrotic syndrome.[25] Other complications inherent with IV administration include IV-access issues.[7,11]

In 2021, using a Markov model, researchers estimated the total *lifetime,* direct medical US cost for an adult patient with severe or moderately severe hemophilia B, according to treatment 3 approaches, as either

- $21,032,332 for treatment with standard half-life FIX prophylaxis,
- $22,933,207 for extended half-life FIX prophylaxis, or
- $20,934,426 for on-demand only FIX treatment.[27]

Prophylactic replacement factor product/treatment accounted for >90% of the total costs in the prophylaxis arms.[27]

Based on data from a cohort of 44 US patients, a separate research group estimated the following annual costs for adults with severe hemophilia B on prophylactic treatment between 2017 and 2019: *mean annual* direct medical cost $614,886 which was primarily driven by FIX treatment; the breakdown per FIX replacement factor class was

- $397,491 for standard half-life product (accounting for 287,141 IU administered in the 1-year period), and
- $788,861 for extended half-life product (accounting for 232,278 IU administered).[15]

The Institute for Clinical and Economic Review (ICER) expressed that US pricing for replacement factor therapies is extremely high due to insufficient market competition and this pricing structure in turn creates "…financial toxicity for patients and their families, financial toxicity for health systems, and builds a platform for pricing potential cures that will only exacerbate these problems."[7] The newly approved gene-therapy may increase market competition but is also a costly treatment.

## 4.2 Recommendations Regarding Gene Therapy (GT)

Principal clinical guidelines (ie, by the World Federation of Hemophilia [WFH] or by the National Hemophilia Foundation's Medical and Scientific Advisory Council) for the treatment of hemophilia B have not been updated since the approval of etranacogene in November 2022. We identified only 1 guideline (international-based) published *after the US approval* of etranacogene that includes limited recommendations regarding gene therapy (GT): the 2022 Recommendations from the German, Austrian, and Swiss Society for Thrombosis and Haemostasis (GAS-STH). Recommendations provided are mostly geared toward the operationalization of GT therapy by hemophilia centers, rather than addressing which patients to select for treatment.[9] The 2022 International Consensus recommendations, published *prior to approval* of etranacogene, included some guidance regarding candidates of GT in the setting of clinical trials.[25]

The 2022 International Consensus (IC) included non-graded, consensus-based recommendations that serve as GT implementation guidance in the context of enrolling clinical studies and its possible future approval.[25] The IC advised, at that time, that GT may be considered as a future treatment option for adults with severe hemophilia B, based on the developing clinical trial data. Authors advised counseling GT candidates on the following aspects[25]:

- "…potential sources of hepatotoxicity that may interfere with FIX expression (e.g. medication use, alcohol)"[25]
- the need for close monitoring of transaminase levels and the possible need for immunosuppression either prophylactically or upon acute liver enzyme elevation following GT administration
- potential side effect profiles of GT and supportive interventions (ie, immunosuppressants)
- "…need for long-term safety and efficacy follow-up, including assessment of liver health and levels of FIX expression, coordinated by the haemophilia centre"[25]
- participation in pharmacovigilance registries to aid in data collection for long-term safety and efficacy evaluations[25]

The GAS-STH recommends use of an electronic platform for secure and instantaneous data exchange between centers of care for GT-treated patients.[9] This would enable the providers involved in a patient's care to follow laboratory parameters, prescribed medications, etc., in real-time. The GAS-STH recommends establishing cooperation agreements that clearly delineate responsibilities of the cooperating centers (ie, to delegate tasks related to follow-up requirements). Suggestions for the immunosuppressive dosing protocol, upon ALT elevation following therapy, are included (see publication for details).[9] Additionally, authors suggest monitoring the following parameters after GT administration and recommend that male patients use physical contraception (condoms) several months following GT administration:[9]

- Alanine aminotransferase (ALT) and factor IX activity: weekly for 6 months; monthly from 6 to 24 months; and then every 6 months thereafter
- Liver ultrasound and fibroscan: annually
- Joint status: biannually

In the absence of clinical guidance from key hemophilia/hematology medical organizations, notably, the Institute for Clinical and Economic Review (ICER) concluded that "…there is moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec compared with factor IX prophylaxis," for the treatment of adults with hemophilia B, following their systematic review.[7]

# 5.0 ETRANACOGENE (HEMGENIX) FOR THE TREATMENT OF HEMOPHILIA B

## 5.1 Indication

Etranacogene is indicated for adults with Hemophilia B (congenital factor IX deficiency) who:

- currently use factor IX prophylaxis therapy, **or**
- have current or historical life-threatening hemorrhage, **or**
- have repeated, serious spontaneous bleeding episodes[8]

While the labeled indication for the product is for the treatment of **adults** with Hemophilia B with the certain aforementioned clinical characteristics, in other sections of the package insert (eg, *Use in Specific Populations*), it is described that this gene therapy is not intended for administration to women (ie, has not been studied in women).[8]

## 5.2 Pharmacology

Etranacogene (Hemgenix) comprises a viral vector that serves to transport functional FIX-encoded gene copies to target cells for expression. The adeno-associated viral (AAV) vector serotype 5 is a non-pathogenic, non-replicating parvovirus. Etranacogene encodes a variant of the naturally occurring human factor IX (Padua R338L variant[†]). Liver cells are the target for delivery of the genetic material. Upon successful transduction of AAV-delivered FIX gene copies, the gene is expressed in liver cells to produce functional FIX protein (via a liver-specific promotor region in the delivered gene) and ultimately increases systemic FIX levels/activity and lessens hemophilia B sequela.

Certain factors can prevent successful transport of AAV-genetic material into the liver cells following administration of the therapy. For instance, if patients have had previous exposure to an adeno-associated virus via natural infection, they may have developed high titer neutralizing antibodies to adeno-associated vectors which, depending on the level, can impede/prevent successful delivery and benefits of the gene therapy.[28] Similarly, patients who have received a dose of etranacogene also develop antibodies to the AAV,[8] which potentially limits AAV-based therapies to a one-time administration opportunity. Sources of hepatotoxicity (eg, heavy alcohol use) may also interfere with the liver's ability to express the functional FIX gene.[25]

In a pharmacokinetic assessment of 10 patients, the maximum observed time for complete clearance of vector genetic material (ie, below the limit of detection) was 22 weeks from urine, 26 weeks from saliva and nasal secretions, 40 weeks from feces, 52 weeks from semen, and 159 weeks from blood. Nonetheless, based on pharmacokinetic data from pivotal clinical studies, the clearance of vector genetic material from semen and blood has been observed to take as long as 2-3 years post-administration in some cases.[8]

## 5.3 Efficacy

Two pivotal clinical trials (phase 2b and phase 3) led to the approval of etranacogene.[20,29,30] Both studies were small, single-arm, open-label trials that **enrolled adult males with FIX activity of ≤2% (ie, moderate-to-severe hemophilia B based on FIX level) regardless of pre-existing AAV5 neutralizing antibody status**. Etranocogene was studied as a single intravenous dose of $2\times10^{13}$ gene copies (gc) per kilogram body weight, with follow-up planned for 5 years.[8]

In the **phase 2b study**,[‡] with 3 patients treated with the full dose of etranacogene, increases in FIX activity were observed for each patient, and the mean FIX activity level (44.2%) remained near normal ranges for 2 years post-administration. The successful conversion of disease severity from severe to mild (per FIX activity level) was unaffected by the presence of pre-existing AAV5 neutralizing antibodies at baseline; all 3 patients had baseline AAV5 antibodies.[29,31] At the 3-year follow-up point, FIX activity levels

[†] Etranacogene is the successor of the gene therapy AMT-060 (with the wild-type human factor IX gene sequence) that included the same AAV5 capsid but differs in the gene-cassette by 2-nucleotides.

[‡] Other inclusion criteria for the phase 2 study were that patients must be receiving prophylactic FIX therapy, or on-demand FIX plus a history of ≥ 4 bleeds per year or chronic hemophilic arthropathy. Exclusion criteria were similar to the phase 3 trial.

were sustained at a mean of 36.9%, and patients were free from steroid use (for purposes of treating liver enzyme elevations) during the long-term follow-up. Patients remained off FIX prophylaxis, were FIX inhibitor free, and did not experience any late-emergent safety events. One patient required several treatments with episodic FIX replacement factor for dental procedures or minor surgeries during the 3-year period.[31,32]

The **phase 3 trial** (Health Outcomes with Padua Gene; Evaluation in Hemophilia B [HOPE-B]; NCT03569891) began in 2018. It includes 54 patients with severe (FIX activity of <1%) or moderately severe (FIX activity of 1 to 2%) and a severe bleeding phenotype,[§] who were administered etranacogene.[20] Patients were required to be on stable continuous FIX prophylaxis for at least 2 months prior to screening. To control for confounding factors, the following key clinical characteristics disqualified patients for inclusion: *uncontrolled* human immunodeficiency virus (HIV) infection, active hepatitis B or C infection, advanced liver fibrosis, history of factor IX inhibitors, or liver or renal laboratory results greater than 2 times the upper limit for AST, bilirubin, ALT, or creatinine.[**] During a 6-month lead-in period while receiving FIX prophylaxis (ie, standard-of-care), bleeding events were recorded to establish the patient's baseline frequency.[20] Baseline characteristics of the included population were the following[20]:

- Annualized bleeding rate of 4.2 episodes
- 81% of patients had a history of FIX activity of <1% at diagnosis; the remainder had moderate severity deficiency (1-2% FIX activity level)
- Mean age: 42 years (range 19-75)
- 39% had detectable neutralizing AAV5 antibodies; the highest observed titer was 1:3212
    - The titer assessment employed an experimental assay that was later determined to be insufficient (not a valid or reliable). A validated assay remains to be developed.[11]
- > 80% "…had a history of joint or bone disease, orthopedic surgery related to hemophilic arthropathy, or both."[20]
- 9 (17%) subjects had prior HBV infection; 28 (52%) had previous HCV infection; 3 (6%) were HIV positive

Following the single dose of etranacogene ($2\times10^{13}$ gc/kg), the primary endpoint was assessed as the annualized bleeding rate during months 7 through 18 post-administration versus the pre-treatment rate (evaluated in a noninferiority analysis).[20] The annualized bleeding rate decreased from **4.2 episodes during the lead-in phase to 1.5 episodes** following treatment (a 64% decrease).[20] This outcome was statistically non-inferior and superior to pre-treatment conditions (ie, standard-of-care with FIX

[§] Severe bleeding phenotype is not further defined in the published study or supplementary materials. Per baseline information, the mean annualized bleeding rate at the end of the 6-week lead in phase was 4.2 bleeds for the included population; yet, 26% of patient had no bleed in the lead-in period, and 19% had no bleed documented 1 year prior to screening.

[**] Additional exclusion criteria to receiving gene therapy included the following: receiving antiviral therapy for hepatitis B or C exposure, other coagulation disorder aside from hemophilia B, thrombocytopenia (platelets <50 × $10^9$/L), severe infection, other significant ongoing uncontrolled medical condition (eg, renal, hepatic, cardiovascular, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease, alcoholism, drug dependency), significant medical condition that could reduce transduction and/or expression of the gene therapy (eg, disseminated intravascular coagulation, accelerated fibrinolysis, profound liver fibrosis), uncontrolled allergic conditions or allergy/hypersensitivity to any component of the treatment, or medical condition requiring chronic administration of steroids.

prophylaxis). Spontaneous bleeding and joint bleeds decreased by 71% and 78%, respectively, following treatment. Data collection is ongoing for this study and will follow patients 5 years from the administration of etranacogene.[20]

**Table 3** below summarizes key annualized bleeding rate outcomes of the trial. Thirty-four patients (63%) had no bleeds following treatment compared to 14 (26%) patients in the lead-in phase. An increase in the mean FIX activity was observed by week 3 following gene-therapy administration and continued to increase until month 6. Activity level was sustained through month 18 (least-squares mean increase from baseline, 34.3%[††]; 95% CI, 29.5 to 39.1).[20] The proportion with FIX activity level <12% at months 12 and 18 was 8% and 6%, respectively (per ClinicalTrials.gov data).[33]

Nearly all patients who received the full dose of etranacogene (52/53, 98%) responded to therapy and were able to discontinue FIX prophylaxis.[20] One patient who had the highest baseline AAV5-antibody titer (of 3212) did not respond to the full dose of etranacogene (ie, FIX activity remained <5% at month 18) and required continuation of factor IX prophylaxis. One patient, of the 54 total included patients, received a small fraction of the dose (~10%) since they prematurely discontinued the infusion upon manifesting a hypersensitivity reaction, but did not respond to the sub-therapeutic dose.[20]

Most subgroup analyses were also consistent with the primary outcome finding at month 18 (eg, subgroups according to age category, baseline bleeding vs. no-bleeding episodes, HIV status, hepatitis history, degree of liver fibrosis/steatosis), the exception being AAV5- antibody positivity vs. negativity at baseline.[34] However, when the single patient with the highest AAV5- antibody titer was excluded from the analysis, the subgroup assessment was consistent with the primary endpoint favoring gene therapy compared to FIX prophylaxis. Investigators concluded that "Up to a titer of 678, no correlation was seen between a participant's preexisting AAV5 neutralizing antibody titer and the participant's factor IX activity at 18 months after treatment."[20]

The annualized consumption of FIX replacement products decreased by 248,825 IU post-treatment (from a mean use of 257,338 IU during the lead-in period), representing a 97% decrease. The patient-annualized FIX infusion rate decreased to 2.5 infusions post-treatment, from 72.5 infusions during the lead-in phase; 15 participants were attributed to FIX infusions during the post-treatment phase.[20]

*Table 3. Phase 3, Key Efficacy Bleeding Rate Results[20]*

| | Baseline, while on factor IX prophylaxis | Month 18 | Relative risk reduction |
|---|---|---|---|
| Annualized bleed rate | 4.19 | 1.51 | 64% |
| Annualized factor IX-treated bleed rate | 3.65 | 0.84 | 77% |
| Annualized spontaneous bleed rate | 1.52 | 0.44 | 71% |
| Annualized joint bleed rate | 2.35 | 0.51 | 78% |

[††] Activity level measured by one-stage activated partial-thromboplastin time–based assay

### 5.3.1 Conference Abstract Information

Conference abstracts presented in 2023 report that the effect of etranacogene on increasing factor activity level was maintained 2 years following administration in the phase 3 study population: the mean level was 36.7% (n=50) at the 2-year follow-up.[35] Furthermore, the annualized bleed rate (ABR; for all bleeds) for months 7 to 24 following administration (of 1.51) continued to be reduced from the baseline ABR (of 4.18) in the full analysis set (n=54). Excluding the 2 non-responders (1 with very high baseline anti-AAV antibodies and 1 who received ~10% of the dose),[36] the intention-to-treat analysis resulted in a reduction of ABR, from 4.00 at baseline to 0.95 for months 7 to 24.[35]

**Table 4** summarizes the factor activity level in the phase 3 trial population over the 2 years of follow-up.

*Table 4. Factor Activity Level, Phase 3 Study Results [11,37]*

| | Baseline | Month 12 | Month 18 | Month 24 |
|---|---|---|---|---|
| Mean factor activity, measured by one-stage aPTT-based assay (% normal) | <2% | 41.5%<br>range 5.9-113.0% | 36.9%<br>range 4.5-122.9% | 36.7 %<br>range 4.7-99.2% |

Health related quality of life (HRQoL) results were reported for the 2-year post-dose follow-up of the phase 3 study.[38,39] Improvements at year 2 versus baseline were identified using the EQ-5D-5L tool (a generic instrument for HRQoL, the EuroQol 5-Dimension 5-Level questionnaire) and a hemophilia-specific instrument (Hemophilia Quality of Life Questionnaire for Adults [Hem-A-QoL]).[38] In contrast, no statistically significant improvements in the EQ-5D-5L score after the first year following gene therapy were initially observed in the phase 3 trial after 18 months.[20] However, improvements were observed in the total score, and in 4 of 10 individual domain scores using the disease-specific Hem-A-QoL tool after the first and second year following gene therapy administration (ie, domains of 'Treatment', 'Feelings', 'Future', and 'Work/School'). Authors concluded that 2 years after gene therapy treatment, "…participants reported reduced treatment burden and feelings consistent with increased optimism for the future."[38]

# 6.0 SAFETY

## 6.1 Adverse Events

According to the prescribing information, the most common adverse reactions with etranacogene, occurring in ≥5% of treated patients in the 2 key pivotal studies (accounting for N= 57 total), were ALT elevation (42% of patients, mostly mild to moderate[20]), AST elevation (42%), blood creatine kinase elevations (42%), infusion-related reactions (33%), headache (18%), flu-like symptoms (14%), fatigue (12%), malaise (12%), and nausea (7%).[8] Notably, the phase 3 trial (N=54) publication reported lower rates for the following AEs: 20% for ALT elevation and 15% for creatinine kinase elevation.[20] Due to vague/limited reporting information in the package insert, the reason for the discrepancy is unclear; however, it is possibly related to different follow-up time frames (eg, 7-18 months post-treatment period for the study publication vs. the entire post-treatment study period for the package insert information).

For the 11 patients with elevated ALT in the phase 3 trial, the mean time to first ALT elevation was 47 days (range 22-120). Nine patients were treated with corticosteroids for the elevation, for a mean duration of 80 days (range 51-130).[40] Investigators summarized, "…supportive care with corticosteroids achieved normalisation of liver transaminase levels and maintenance of most pre-steroid levels of FIX, avoiding return to FIX prophylaxis."[40]

In the phase 3 study, there were 87 moderate adverse events (AEs) and 14 severe AEs reported over the 12-month follow-up. However, none of the 14 serious AEs were considered treatment-related by the investigators. No thromboembolic events were reported. Three participants experienced infusion-related AEs of special interest (eg, eye pruritus, urticaria, chest discomfort, dizziness, flushing), for which the drug infusion was temporarily interrupted in order to resolve/recover from the reaction (with the help of medications [eg, antihistamine, corticosteroid]). One patient (separate from the 3 aforementioned patients) discontinued the infusion prematurely, thus receiving only a partial dose, due to manifestation of a moderate hypersensitivity reaction; the patient eventually recovered.[20]

## 6.2 Warnings and Precautions

- ***Infusion reactions:*** Hypersensitivity reactions and anaphylaxis have been reported, along with other reaction symptoms (eg, chest tightness, headaches, abdominal pain, lightheadedness, flulike symptoms, shivering, flushing, rash, and hypertension). Patients should be monitored during gene-therapy administration and at least for 3 hours after completion of the infusion. To minimize reaction symptoms, the product should be infused at a rate of ≤500 mL/hr. In the event of reactions, corticosteroids or antihistamines may be considered and the infusion rate may be slowed or interrupted and re-started at a slower infusion once reaction symptoms have resolved.[8]

- ***Hepatotoxicity***: Elevation of liver enzymes (ie, transaminitis) observed within 3 months after etranacogene administration "…is presumed…" to be due to an immune-mediated reaction/injury of transduced hepatocytes. This reaction may reduce the efficacy of the gene therapy. Liver enzyme monitoring is recommend as described in the following section (section 6.3).[8] The time to resolution of elevated liver enzymes is highly variable, ranging from days to a year or more.[8,28]

- ***Hepatocellular carcinogenicity***: There is a *theoretical* risk of the development of hepatocellular carcinogenicity with gene therapy transduction of hepatocytes. Liver health in patients with preexisting risk factors should be monitored (ie, annually for 5 years) using liver ultrasound and alpha-fetoprotein testing.[8]

- **Anti-AAV5 capsid neutralizing antibodies**: Candidates planning to receive etranacogene are encouraged to enroll in a planned study that will measure/evaluate the effect of pre-existing anti-AAV5 neutralizing antibodies on the treatment outcomes. Currently, there is no validated anti-AAV5 antibody assay.[8] Many patients enrolled into the clinical studies had AAV antibodies at baseline; moreover, all patients treated with the AAV-based gene therapy developed post-treatment AAV antibodies.[8]

    - In the phase 3 trial, improvement of FIX activity following gene therapy was maintained irrespective of preexisting AAV5-neutralizing antibodies up to titers of 678 (using a luciferase-based assay).[20] Earlier preclinical studies in non-human primates showed that the efficacy of AVV5 GT was not significantly impacted by AAV5 neutralizing titers up to 1:1030.[41]

- **Monitor** for FIX activity and inhibitors as described in the following section (section 6.3).

## 6.3 Monitoring

The following laboratory monitoring is recommend, per the prescribing information (package insert) following the administration of etranacogene[8]:

- ✓ Monitor for infusion reactions during administration and for at least 3 hours following administration. If a reaction occurs during infusion, the rate can be slowed or interrupted, then resumed at a slower rate as appropriate.
- ✓ Regular liver enzyme monitoring is required to catch signs of immune-mediated hepatotoxicity
    - Test weekly for 3 months; continue monitoring in patients with sustained elevated liver enzymes until values return to baseline. Consider administration of corticosteroids with ALT > normal limits, or twice the patient's baseline within the first 3 months post-dose; FIX activity level should also be monitored during liver enzyme elevation.
- ✓ Monitor factor IX activity (ie, weekly for the first 3 months after administering etranacogene)
    - When exogenous FIX is administered, patients should also be monitored.
        - Note that "…it may take several weeks before improved hemostatic control becomes apparent after HEMGENIX infusion; therefore, continued hemostatic support with exogenous human Factor IX may be needed during the first weeks after HEMGENIX infusion."[8]
    - If possible, use the same assay and reagents when monitoring FIX changes, since variation in assay readings may give discrepant information.
- ✓ Conduct regular alpha-fetoprotein (AFP) testing and abdominal ultrasound (eg, annually) in patients with preexisting risk factors for hepatocellular carcinoma.
    - Risk factors include cirrhosis, advanced hepatic fibrosis, hepatitis B or C, non-alcoholic fatty liver disease (NAFLD), chronic alcohol consumption, non-alcoholic steatohepatitis (NASH), and advanced age.

- ✓ Monitor for the development of factor IX inhibitors post-dose as indicated (eg, clinical observation or laboratory assessment if there are signs [eg, bleeding uncontrolled with factor FIX products or if plasma factor IX activity levels decrease])

## 6.4 Special Populations

***Liver Impairment***: Etranacogene was not studied in patients with advanced liver impairment, including cirrhosis, advanced liver fibrosis, or uncontrolled Hepatitis B and C. In studied patients with other degrees of hepatic impairment, FIX activity was numerically lower compared to patients without impairment. Patients with hepatic steatosis were studied and found to have improved FIX activity levels at 6 through 24 months post-dose: mean factory IX activity, as measured by one-stage aPTT assay, ranged from 35 to 28 over the 24 months.[8]

***Renal Impairment***: Etranacogene was not studied in patients with severe renal impairment (creatinine clearance = 15 to 29 mL/min) or end-stage renal disease (creatinine clearance < 15 mL/min); however, patients with mild to moderate renal impairment were studied. Patients with mild impairment expressed approximately 37% higher FIX activity versus those with normal renal function upon administration of the gene therapy. The single patient with moderate renal impairment expressed similar FIX activity compared to subjects with normal renal function.[8]

***Pediatric Use***: Etranacogene is not established for use in the pediatric population.

***Geriatric Use***: In the 6 geriatric patients studied, there were no meaningful differences in the safety and efficacy of etranacogene therapy (at the same dose) compared to younger patients.

# 7.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION CRITERIA

The following prior authorization criteria (and/or educational notes) may be considered for the Hemgenix (etranocogene) authorization form.

- ✓ Adults, age ≥18 years
  - Hemgenix use is not established in pediatric patients at this time

- ✓ Requirement for a diagnosis of **severe or moderately severe hemophilia B** (ie, factor IX level historically documented as ≤2% of normal by a one stage [aPTT based] assay while the patient was untreated by replacement factor).
  - The labeled indication for Hemgenix is for the treatment of hemophilia B (HB) without specification of a particular disease severity. Patients included in the phase 3 trial for Hemgenix had moderately severe to severe HB disease as defined by a history of factor activity level of ≤2% while untreated with replacement factors. Experimental studies have not determined the efficacy and safety in patients with higher baseline FIX activity levels (ie, mild or moderate hemophilia B activity level). The effect of gene-therapy is highly variable with respect to the increase of factor levels in individual patients, as illustrated by the wide ranges in Table 4. Hypothetically, higher baseline activity levels *may* predispose the patient to concerning levels above 100% normal.

- ✓ Patient meets at least 1 of the following criteria, per labeled indication:
  - currently uses factor IX **prophylaxis** therapy, or
  - has current or past history of life-threatening hemorrhage, or
  - has had repeated, serious spontaneous bleeding episodes

- ✓ Per product labeling, the following laboratory assessments should be completed in order to assess/determine the patient as a candidate for treatment. Thus, the prescriber should attest that the following assessments have been recently performed:
  - Factor IX inhibitor titer testing: the patient should not be positive for FIX inhibitors (ie, with 2 positive results within 2 weeks; see package insert)
  - Liver health assessments, including each of the following: AST, ALT, bilirubin, hepatic ultrasound, and hepatic elastography

- ✓ Prescriber is a hematologist.

- ✓ In the case of pre-treatment radiological liver abnormalities and/or sustained liver enzyme elevations, a hepatologist has also evaluated and confirmed the patient's candidacy for the therapy.

- ✓ Attestation that the patient does not have any of the following medical conditions that were exclusion criteria for the pivotal clinical trial, since they could theoretically decrease the efficacy of the treatment by impairing cellular transduction and the liver's ability to express the therapeutic gene:
  - uncontrolled alcohol use disorder or uncontrolled substance use disorder

- uncontrolled HIV (eg, controlled disease is considered CD4+ counts ≥200/uL and/or HIV viral load ≤200 copies/mL)
- accelerated fibrinolysis, profound liver fibrosis, or disseminated intravascular coagulation
- receiving treatment for (or active infection of) hepatitis B or C
- active severe infection

✓ Attestation that the prescriber has provided the following counseling in order to promote realistic patient expectations (ie, patients should not expect a cure per se) and to ensure that the patient accepts the monitoring requirements, potential side-effect risks, and prudent life-style precautions:

- Patient has been counseled on the potential need for and side effects releted to immunosuppressive therapy and the possibility of long-term or multiple treatment courses for the management of elevated liver enzymes (a common side effect of this gene therapy).
  - In a survey of patients who received AAV-based gene-therapy for hemophilia (eg, etranacogene or others) in pivotal clinical trials, side effects of immunosupression (for the treatment of elevated liver enzymes) that were burdensome and/or surprising to patients included feelings of depression, insomnia, mood changes, anger, and weight gain.[42]
- Patient understands that FIX treatment may still be required in the future, in the event of nonresponse to gene-therapy, episodic breakthrough bleeds, or for perioperative management.
- Patients should be notified that receiving this AAV gene therapy may disqualify them from receiving other AAV gene therapies that may come to market in the future. High-titer neutralizing anti-AAV antibodies develop after AAV vecor administration; thus, patients would likely have pre-existing antibodies to AAV vectors thereafter.
- The prescriber and patient should be cognizant of potential factors that may theoretically diminish the liver's expression of the therapeutic gene. It may be most prudent to avoid heavy alcohol intake; however, such directive is not included in the prescribing information.[7,25]
- While no directive is provided in the package insert, it may be most prudent for treated males to use barrier contraception (condoms) as applicable during the initial years after administration while the vector is cleared via semen.[7]

✓ The prescriber attests that they will follow monitoring recommendations at least as frequently as inidicated in the package insert (as outlined in section 6.3), and will also consider continued monitoring for ALT (eg, monthly till month 24, then every 6 months thereafter) as suggested by experts of the German, Austrian, and Swiss Society for Thrombosis and Haemostasis (GAS-STH).

✓ Coverage authorization is for a single, life-time dose only. The patient should have no history of prior etranacogene treatment, and the dose should be consistent with the weight-based labeled dosage.

- At this time, etranacogene has been established as a single life-time dose. Studies are not avaiable to establish additional doses of therapy for when factor activity response begins to decline below adequate levels.

- ✓ An educational note on the PA form may be included to direct prescribers to contact CSL Behring (1-833-436-0021) in order to access the assay for detection of anti-AAV antibodies. Such assessment/results may help guide the decision of administering Hemgenix.

**Other Considerations**

*FIX replacement therapy following etranacogene treatment*:

Although etranacogene therapy has a high potential to convert patients from a severe factor deficiency (ie, <2% FIX activity) to more mild deficiency (>5% FIX activity; mean activity level sustained at 36.7% at the 2-year follow-up in patients treated in the phase 3 trial),[35] patients may still require pre-operative prophylaxis and perioperative management with FIX replacement factors for surgeries. Additionally, responders to therapy may still require episodic treatment with FIX replacement factors for occasional breakthrough, spontaneous or traumatic bleeds. Prophylactic therapy will need to be continued in the very few non-responders and in cases that may lose the treatment effect (eg, due to loss of transduced hepatocytes).

- Even though patients may express higher FIX activity levels following gene therapy treatment, activity levels may still be lower than the desired target for perioperative procedures. Target FIX activity ranges for perioperative management of patients with hemophilia B are consolidated in the WFH guideline, table 7-2.[1] For example the pre-operative peak target range is 50-70% for a major surgery, and 40-80% for a minor surgery.[1]
- Based on information reported in a conference abstract, of the patients treated in the phase 2b and phase 3 studies with etranacogene, over the 3- and 2-year follow-up periods, respectively, exogenous FIX prophylaxis, either as standard or extended half-life product, was used prior to surgery for 5/18 (28%) dental procedures, 7/18 (39%) minor surgeries and 20/22 (91%) major surgeries. Authors described that there were no safety issues with these cases treated with FIX replacement factors for perioperative management, no inhibitors developed, and no thrombotic events occurred.[32]
- Patients will need to continue their prophylactic therapy until factor activity level rises to adequate levels following GT administration. The time it takes for this is variable. In the phase 3 trial, efficacy was not assessed until after 6 months post-administration. However, frequent monitoring of factor activity is still required immediately following GT administration.

*Neutralizing AAV-antibodies*:

Neutralizing antibodies may be pre-existing in a given patient due to a previous natural infection with wild-type AAV. Anti-AAV antibodies to the GT are of potential concern since they could theoretically impede efficacy. In the phase 3 study for etranacogene, positive neutralizing antibody status was not an exclusion factor: 39% of enrolled patients had detectable neutralizing AAV5 antibodies at baseline. Of these, only the patient with the highest titer level (1:3212) did not respond to the full dose of etranacogene. Investigators concluded that "Up to a titer of 678, no correlation was seen between a participant's preexisting AAV5 neutralizing antibody titer and the participant's factor IX activity at 18 months after treatment."[20] Nonetheless, at this time, no validated anti-AAV antibody assay exists. The assay used in the clinical trial was an experimental assay eventually determined to be insufficient (not a valid or reliable) by the FDA.[11] Regardless, the pharmaceutical company of Hemgenix expresses in resources for prescribers that if the prescriber wishes to test their patient for anti-AAV antibodies, "CSL

Behring will make available a laboratory developed, CLIA-validated test that was used during the clinical trial."[43]

*Women with childbearing potential:*

Hemophilia B primary occurs in males (ie, >95% of cases). Likely due to the rarity in females and associated recruitment limitations, females were not included in the clinical trials for Hemgenix. The *Pregnancy and Lactation* sections of the product package insert express that the gene-therapy is not intended for women. Nonetheless, there is not a labeled contraindication for this population, and the formal indication does not name males only (ie, indicated for adults). It is unclear what the FDA and/or sponsor's specific rationale was for not intending the gene-therapy for women, and whether it has to do more specifically with childbearing potential. The approval review of the European Medicines Agency (EMA), does express a theoretical concern *specific* to women of childbearing potential (eg, rare possibility of viral vector integration to fetal cells).[44] Since no data were available to inform this theoretical concern (eg, animal fertility/embryofetal studies), the EMA does not recommend the Hemgenix for women of childbearing potential, during pregnancy, or during lactation.[44]

# 8.0 SUMMARY

Prior to the availability of gene-therapy, hemophilia B has been managed with replacement factor IX (FIX) therapy. Prophylactic FIX regimens are the standard of care for patients with more severe disease; however, such regimens require burdensome, frequent self-administrations of intravenous replacement factor products (ie, twice weekly to every other week, depending on the product) and strict adherence to maintain adequate factor levels. Despite advances that extend FIX product half-life, residual breakthrough bleeding and long-term joint or organ damage can occur and negatively impact quality of life. Etranacogene (Hemgenix) gene therapy has been developed with the goal to normalize FIX levels via consistent and durable expression of the adeno-associated virus (AAV)-delivered healthy FIX gene.[38]

Thus far, etranacogene is established for adult men with baseline FIX levels of ≤2% (untreated) and without advanced liver disease. The single-arm, phase-3 study with before/after assessment supported the approval of etranacogene. The mean annualized bleeding rate and consumption of FIX replacement product decreased by 64% and 97%, respectively, in the post-treatment time period (months 7-18) compared to baseline on standard-of-care treatment (ie, FIX prophylaxis). Corresponding increases and maintenance of near normal FIX activity levels (eg, 37% mean factor activity) were demonstrated at 18 months and 2 years following treatment. Of patients receiving the full therapeutic dose of etranacogene, one patient did not respond to therapy. This patient had the highest AAV5 antibody pre-treatment titer (of 3213). Other patients with AAV5-antibody pre-treatment titers of 678 or lower did respond to therapy, and of these, all who received the full dose of etranacogene were able to discontinue FIX prophylaxis. The other non-responder did not receive the full dose of etranacogene—only about 10% of the dose—since treatment was stopped prematurely due to hypersensitivity reaction.[20]

Adverse events of etranacogene were primarily considered mild. Concerning side effects include elevated blood liver enzymes that may require short- or long-term corticosteroid treatment, and infusion-related reactions that may require supportive interventions and may possibly prevent delivery of the full dose or etranacogene. Hepatotoxicity is possible with AAV-based gene therapies in general

but can be managed with corticosteroids. Hepatotoxicity is concerning regarding liver health and the maintenance of the gene-therapy effect; transduced hepatocytes can be lost if such reaction is not promptly treated with corticosteroids. Post-treatment monitoring of liver enzymes is recommended weekly for 3 months, but because the reaction can manifest beyond 3 months, ongoing monitoring is prudent to help ensure the durability of transduced hepatocytes.

While nearly all patients treated with etranacogene were able to discontinue FIX prophylaxis, patients may still require perioperative replacement factor therapy and episodic treatment for breakthrough bleeds; thus, etranacogene should not be pitched as a cure to candidates. Moreover, it remains to be determined whether the substantial increase in factor IX levels following etranacogene treatment will persist for decades or lifelong. Treated patients are encouraged to participate in long-term follow-up studies. While there are burdens with FIX prophylaxis, there are also burdens associated with gene therapy. Patients should be counseled thoroughly to align expectations with possible outcomes, frequent monitoring requirements, side effects of etranacogene, and potential need of long-term corticosteroids. Prior authorization criteria are proposed for etranacogene (see section 7.0) according to the population that efficacy/safety were demonstrated in; labeled recommendations regarding the indication for therapy, baseline screening for liver health and FIX inhibitors, and ongoing monitoring; and counseling points. This highly specialized, costly therapy should be prescribed by a specialist (ie, hematologist) and may require consultation with a hepatologist in the event of pre-treatment radiological liver abnormalities and/or sustained liver enzyme elevation.

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# APPENDIX A – SEARCH STRATEGIES

## GUIDELINE SEARCHES

**Ovid Medline:** *Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 03, 2023*

h?emophilia.ti. AND ((position statement* or policy statement* or practice parameter* or best practice* or guideline* or CPG or CPGs or standards* or consensus* or recommendat* or (care adj2 (standard* or pathway* or map* or plan*)) or (algorithm* adj2 (pharmacotherap* or therap* or treatment* or intervention*))).ti,pt.)

- Results limited to **2015** onward (93)

h?emophilia.ti. AND (exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or Clinical Decision Rules/ or (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. or (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf. or (standards or guideline or guidelines).ti,kf. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,kf. or consensus*.ab. /freq=2 or ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf. or recommendat*.ti,kf. or guideline recommendation*.ab. or (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf. or (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf. or (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf. or (guideline* or standards or consensus* or recommendat*).au.)

- Results limited to 2020 onward (114)

**Embase:** *May 25th, 2023*

(hemophilia:ti OR haemophilia:ti) AND ('position statement*':ti OR 'policy statement*':ti OR 'practice parameter*':ti OR 'best practice*':ti OR guideline*:ti OR cpg:ti OR cpgs:ti OR standards*:ti OR consensus*:ti OR recommendat*:ti OR ((care NEXT/2 (standard* OR pathway* OR map* OR plan*)):ti) OR ((algorithm* NEXT/2 (pharmacotherap* OR therap* OR treatment* OR intervention*)):ti))

- ✓ Results limited from 2021 onward (56)

## Additional Evidence Search

**Ovid Medline:** *Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 30, 2023*

((etranacogene or Hemgenix or (gene-therapy and (h?emophiliaB or h?emophilia-B))).ti,ab.)

OR

Hemophilia B/ and Genetic Therapy/

- ✓ Results limited to 2022-2023 **(65)**

**Embase:** *May 30th, 2023*

| No. | Query | Results |
|---|---|---|
| 1 | (etranacogene:ti,ab OR hemgenix:ti,ab OR ('gene therapy':ti,ab AND (h?emophiliab:ti,ab OR 'h?emophilia b':ti,ab))) AND [2022-2023]/py | 48 |
| 2 | 'gene therapy agent'/exp AND 'hemophilia b'/exp | 970 |
| 3 | 'etranacogene dezaparvovec'/exp | 114 |
| 4 | #2 OR #3 | 981 |
| 5 | #1 OR #4 | 997 |
| 6 | (#1 OR #4) AND [2022-2023]/py | **109** |