| Policy and Procedure | |
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| **PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH050.1025** | **MISCELLANOUS PRODUCTS**<br>**GENE THERAPY FOR HEMOPHILIA**<br>See Table 1 for medications covered by policy |
| **Effective Date: 1/1/2026** | **Review/Revised Date**: 08/23, 10/23, 08/24, 08/25 (MTW) |
| **Original Effective Date: 04/23** | **P&T Committee Meeting Date**: 02/23, 10/23, 12/23, 10/24, 10/25 |
| **Approved by:** Oregon Region Pharmacy and Therapeutics Committee | |

**SCOPE:**
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

**APPLIES TO:**
Commercial
Medicare Part B
Medicaid

## POLICY CRITERIA:

**COVERED USES:**
All Food and Drug Administration (FDA)-Approved Indications

**REQUIRED MEDICAL INFORMATION:**
Gene therapy may be approved when all the following criteria are met:

1. One of the following:
    a. For Beqvez® (fidanacogene elaparvovec) or Hemgenix® (etranacogene dezaparvovec) requests: Diagnosis of severe or moderately severe hemophilia B, defined by one of the following: Factor IX level less than 2 IU/dL or less than or equal to 2% of normal, provider attestation, or prior records of moderate to severe hemophilia B
    b. For Roctavian® (valoctocogene roxaparvovec) requests: Diagnosis of severe hemophilia A, defined by Factor VIII level less than 1 IU/dL or less than or equal to 1% of normal
2. One of the following:
    a. Patient is currently on a stable dose of prophylaxis therapy (has been receiving prophylaxis for two months or more) with greater than 150 exposure days of prophylaxis
    b. Current or historical life-threatening hemorrhage
    c. Documentation of repeated, serious spontaneous bleeding episodes
3. Patient is negative for Factor inhibitors, defined by a Factor inhibitor level assay less than 0.6 Bethesda units (BU) per mL. If initial test is positive, documentation of a subsequent negative test within 1-4 weeks will be allowed

4. Provider attestation that patient has been tested for appropriate adeno-associated virus (AAV) antibodies and is deemed a suitable candidate for treatment. See Table 1 for specific adeno-associated (AAV) virus antibodies according to the therapy requested
5. Gene therapy will be administered by or in consultation with a Hemophilia Treatment Center (HTC)
6. For Commercial Beqvez® (fidanacogene elaparvovec) requests: The patient has a contraindication to Hemgenix® (etranacogene dezaparvovec)

**EXCLUSION CRITERIA:**

- HIV not controlled with antiviral therapy (CD4+ counts equal to 200/µL or by a viral load of greater than 200 copies/mL)
- Active hepatitis B or C infection, unless evaluated by hepatology
- Evidence of advanced liver fibrosis (Fibroscan score of 9 kPA or greater)
- ALT, AST, total bilirubin, alkaline phosphatase, or creatinine greater than two times the upper limit of normal, unless evaluated by hepatology
- Previous treatment with gene therapy for the same indication

**AGE RESTRICTIONS:**
May be approved for patients aged 18 years and older.

**PRESCRIBER RESTRICTIONS:**
Must be prescribed by, or in consultation with, a hematologist.

**COVERAGE DURATION:**
Authorization will be limited to one treatment course per lifetime.

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*Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047*

*Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.*

*Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.*

*Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case*

| PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH050 | MISCELLANOUS PRODUCTS<br>GENE THERAPY FOR HEMOPHILIA<br>See Table 1 for medications covered by policy |
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**INTRODUCTION:**
Etranacogene dezaparvovec-drlb (Hemgenix®) is an adeno-associated virus serotype 5 (AAV5) based gene therapy designed to deliver a copy of a transgene encoding the Padua variant of human coagulation Factor IX (hFIX-Padua). A single intravenous infusion results in cell transduction and an increase in circulating Factor IX activity.

- The recommended dose is 2 x $10^{13}$ genome copies (gc) per kg of body weight, administered as a one-time intravenous infusion.

Fidanacogene elaparvovec-dzkt (Beqvez®) is an adeno-associated virus vector-based gene therapy designed to deliver a copy of a transgene encoding a high-activity variant factor IX gene (known as the Padua variant). A single intravenous infusion results in cell transduction of hepatocytes and an increase in circulating Factor IX.

- The recommended dose is 5 X $10^{11}$ vector genomes (vg) per kg of body weight, administered as a one-time intravenous infusion.
    - For patients with a BMI ≥ 30 kg/$m^2$ the dosing weight will be calculated as: dosing weight (in kg) = 30 kg/$m^2$ X (height in meters)$^2$. Otherwise actual body weight should be used.

Valoctocogene roxaparvovec-rvox (Roctavian®) an adeno-associated virus serotype 5 (AAV5) based gene therapy vector, designed to introduce a functional copy of a transgene encoding the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). Transcription of this transgene occurs within the liver, using a liver-specific promoter, which results in the expression of hFVIII-SQ. The expressed hFVIII-SQ replaces the missing coagulation factor VIII needed for effective hemostasis.

- The recommended dose is 6 × $10^{13}$ vector genomes (vg) per kg of body weight, administered as a one-time intravenous infusion.

**FDA APPROVED INDICATIONS:**
**Etranacogene dezaparvovec-drlb (Hemgenix®)** is indicated for the treatment of 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.

**Fidanacogene elaparvovec-dzkt (Beqvez®)** is indicated for the treatment of adults with moderate to severe hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated spontaneous bleeding episodes, and

- Do no have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test.

**Valoctocogene roxaparvovec-rvox (Roctavian®)** is indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.

In the pregnancy and lactation sections their respective FDA labeling, it is noted that etranacogene dezaparvovec, fidanacogene elaparvovec, and valoctocogene roxaparvovec are not intended for administration in women.

**POSITION STATEMENT:**
**Hemophilia B**

- Hemophilia B is a recessive X-linked coagulation disorder causing a deficiency of coagulation factor IX (FIX). Occurring primarily in males, the estimated prevalence in the United States is 3.7 cases per 100,000 males, occurring in about 1 per 19,283 male births[6]. Severity is dependent on the level of FIX produced by the patient, with about 44% of patients having severe disease (FIX < 1IU/dL, or <1% of normal). Patients with hemophilia B can experience lifelong spontaneous hemorrhaging into joints, muscles, and soft tissues, which leads to inflammation, pain, and joint damage. Depending on the severity, people with hemophilia can have substantial disability, and life-threatening bleeding following injuries or surgeries may occur.
- Factor IX concentrate is used in patients with moderate to severe hemophilia B as prophylaxis therapy to prevent bleeds and prevent long-term adverse joint effects. Prophylaxis is done to provide sufficient levels of FIX to prevent spontaneous bleeding and requires regular infusions (up to three times a week). About 1-4% of patients with severe hemophilia B develop an antibody to FIX replacement therapy[8], called an inhibitor.

**Hemgenix® (etranacogene dezaparvovec)**
Clinical Trials:
*HOPE-B (NCT03569891)*

- Phase 3 prospective, open-label study consisting of a 6-month lead-in period until treatment, followed by monthly follow-up until month 12 and included an on-going follow-up period of 5 years. Participates were all adult males (N=54) 19 to 75 years old with moderate to severe hemophilia B (FIX levels of ≤2% of normal) that had received continuous prophylaxis for ≥2 months and had >150 previous exposure days of treatment with Factor IX protein. Individuals were excluded if that had FIX inhibitors, active hepatitis B/C infection, uncontrolled HIV infection,

evidence of advanced liver fibrosis, or previous gene therapy 60 days prior to trial.

- All 54 patients received a single intravenous dose of $2 \times 10^{13}$ gc/kg body weight of etranacogene. The primary endpoint was a non-inferiority test of annualized bleeding rate (ABR) during months 7 to 18 after etranacogene treatment compared with the ABR during the lead-in period, which consisted of at least six months of receiving standard of care routine Factor IX prophylaxis. Key secondary endpoints included FIX activity measured by one-stage assay at six, 12 and 18 months after dosing, and FIX consumption.
- Efficacy: The estimated mean ABR during Months 7 to 18 after treatment was 1.9 bleeds per year [95% CI: 1.0, 3.4], compared with an estimated mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period. The ABR ratio (Months 7 to 18 post-treatment / lead-in) was 0.46 [95% CI: 0.26, 0.81], demonstrating non-inferiority of ABR during Months 7 to 18 compared to the lead-in period.

**Total bleeding events and ABRs (Full Analysis Set: N = 54)**

| | Lead-in Period | Months 7 to 18 after treatment |
| --- | --- | --- |
| All bleeds | 136 | 96 |
| Follow-up time (Person-Year) | 33 | 52 |
| Mean adjusted ABR (95% CI) | 4.1 (3.2, 5.4) | 1.9 (1.0, 3.4) |
| Subjects with bleeds | 40 (74%) | 20 (37%) |
| Subjects with zero bleeds | 14 (26%) | 34 (63%) |
| Observed spontaneous bleed count (proportion of total bleeds) | 50 (37%) | 14 (26%) |
| Observed joint bleed count (proportion of total bleeds) | 77 (57%) | 19 (35%) |

  - Secondary endpoints:
    - Mean (SD; min, max) FIX activity was 39.0 IU/dL (±18.7; 8.2, 97.1) at six months and 36.9 IU/dL (±21.4; 4.5, 122.9) at 18 months
    - An overall 97% reduction in FIX consumption from lead-in to seven to 18 months post-treatment, mean (SD) difference in FIX consumption was –248,825 (21,102) IU/year/participant (P<0.0001)
    - 52 out of 54 (96.3%) of participants were able to stop prophylactic FIX infusions. None of the 52 participants returned to prophylaxis during study period
- Adverse reactions following treatment with etranacogene: alanine aminotransferase increased (24 subjects, 42%), headache (10 subjects, 18%), blood creatine kinase increased (24 subjects, 42%), flu-like symptoms (8 subjects, 14%), infusion-related reactions (19 subjects, 33%), fatigue (7 subjects,

12%), aspartate aminotransferase increased (24 subjects, 42%), nausea (4 subjects, 7%), malaise (7 subjects, 12%)

*AMT-061-01 (NCT03489291)*

- Phase 2b, open-label, dose-confirmation/safety trial conducted over 52 weeks with long-term follow-up assessments over 4 years. Participants were all adult males (N=3) with moderate to severe hemophilia B (FIX activity ≤2% of normal) receiving either prophylactic FIX, or on-demand FIX with ≥4 bleeds/year or chronic hemophilic arthropathy (defined as pain, joint destruction, and loss of range of motion in ≥1 joint as assessed by individual investigators). Individuals were excluded if that had FIX inhibitors, active hepatitis B/C infection, uncontrolled HIV infection, or select laboratory values greater than 2 time the upper limit of normal. All 3 participants were administered a single, 500-mL IV infusion of $2 \times 10^{13}$ gc/kg infused over 1 hour
- Primary endpoint: To confirm whether a single dose of $2 \times 10^{13}$ gc/kg of etranacogene would result in FIX activity levels ≥5% at 6 weeks after dosing. Key secondary endpoints: FIX activity at other time points, bleeding rates, and the use of FIX replacement therapy
- Efficacy:

| | FIX activity (% of normal) | | | |
| --- | --- | --- | --- | --- |
| | **Prior to treatment** | **Week 6** | **Week 12** | **Week 26** |
| **Participant 1** | 1 | 37.8 | 37.9 | 51.0 |
| **Participant 2** | <1 | 23.9 | 24.9 | 33.2 |
| **Participant 3** | <1 | 30.0 | 51.1 | 57.0 |

  - In the year prior to treatment with etranacogene, all three participants received prophylactic FIX replacement plus additional doses of FIX for treatment of bleeding events (participants 1, 2, and 3 experienced 3, 1, and 5 bleeds requiring FIX treatment, participant 3 also reported a suspected bleed during the screening period). There were no reported bleeds and no requirement for FIX replacement up to 26 weeks post treatment with etranacogene. As part of the study protocol, participant 1 received two doses of short-acting FIX (on the day of dosing and day three posttreatment), and the other two participants each received 1 dose of short-acting FIX on the day of dosing.
- Safety: Two adverse events determined to be possibly related to treatment with etranacogene occurred: Participant 1 reported a headache on the day of dosing and had a mild elevation in C-reactive protein level on day 14 post-treatment (7.4 mg/L; reference range 0-3 mg/L) that resolved without intervention.

**Beqvez® (fidanacogene elaparvovec)**

Clinical Trials:

BENEGENE-2 (NCT03861273)

- Phase III, single-arm, open-label, multi-center study observing the annual bleeding rate (ABR) of patients both before and after administration of fidanacogene elaparvovec.
  - Patients were included in the trial if they: were a participant in the BENEGENE-1 lead-in study, had previous experience with FIX therapy (≥50 exposure days), had FIX activity ≤ 2%, were male gender, and were ≥18 and <65 years of age
  - Patients were excluded from the trial if they had: presence of factor IX inhibitor, anti-AAV antibodies, previous decreased response to factor IX replacement, significant liver fibrosis, liver disease, active HIV/hepatitis B/hepatitis C infection, LFT abnormalities, or previous hypersensitivity to a factor IX replacement product.
- Results reported are an interim analysis that was included in the package insert for fidanacogene elaparvovec with statistical review and direction from the U.S. Food and Drug Administration (FDA)
- Primary Endpoint: Annual bleeding rate (ABR) compared to Factor IX prophylaxis lead-in trial (BENEGENE-1)
  - Compared minimum of six months of data from BENEGENE-1 lead-in study with week 12 through to month 15 post gene therapy administration in BENEGENE-2 (known as the efficacy evaluation period [EEP]).
  - The planned total follow-up is six years post gene therapy.
- **Total bleeding events and ABRs (Full Analysis Set: N = 45)**

| | **Lead-in Period** | **Week 15 to month 15 after treatment** |
| --- | --- | --- |
| Total number of observed bleeds | 225 | 98 |
| Follow-up time (Person-Year) | 59 | 83 |
| Median (min, max) ABR [bleeds/year] | 1.3 (0.0, 53.9) | 0.0 (0.0, 19.0) |
| Model derived* ABR [bleeds/year] (95% CI) | 4.5 (1.9, 7.2) | 2.5 (1.0, 3.9) |
| Subjects with zero bleeds | 13 (29%) | 27 (60%) |
| Observed spontaneous bleed count (proportion of total bleeds) | 157 (70%) | 60 (61%) |
| Observed joint bleed count (proportion of total bleeds) | 184 (82%) | 71 (72%) |

* A total of 7 participants (16%) had used factor IX replacement products during the efficacy evaluation period for extended prophylaxis that confounded the treatment effect of BEQVEZ,

with a median start time at 0.8 (range: 0.4 to 1.1) years. An ABR of 20 bleeds/year was imputed for the confounded periods.

- Secondary Endpoints
  - Number of patients able to remain off Factor IX prophylaxis (at month 15): 29 (64.4%)
  - Annualized infusion rate (AIR) of Factor IX products was reduced by 92% ($p < 0.0001$) compared to Factor IX use in the lead-in study.
- Adverse Events
  - Overall, fidanacogene elaparvovec was well tolerated. Increased transaminases occurred in 53.3% of patients. No other adverse event was reported in more than 5% of patients. 62.2% of patients received corticosteroids to manage post-infusion cellular immune response to the AAV vector.

**Hemophilia A**

- Hemophilia A is an X-linked recessive inherited disorder leading to deficiencies of one of the proteins necessary for normal blood clothing, factor VIII (FVIII). Affecting predominately males, the estimated number of males living with hemophilia (A or B) in the United States is between 30,000-33,000[12] with approximately 76% of them having hemophilia A. About 60% of these individuals have the severe form of the disorder[13], which is defined as less than 1% of baseline clotting factor activity. Individuals with hemophilia (particularly those with severe disease) are at risk for life-threatening bleeding, including intracranial bleeding. Individuals often have bleeding following an injury, however, may also have frequent spontaneous bleeding episodes, most commonly into the joints (hemarthrosis) or muscles. Joint and muscle bleeds occur most frequently and can lead to substantial disability.
- Prophylaxis with plasma-derived or recombinant standard half-life factor, extended half-life factor, or non-factor replacement emicizumab (Hemlibra®) to prevent bleeding is the current standard of care of patients with severe hemophilia to prevent musculoskeletal complications from recurrent joint and muscle bleeds[14,15]. This is typically started early in life before the age of 3. Patients who develop inhibitors may eradicate inhibitors through immune tolerance induction (ITI) therapy. Patients who do not respond to enhanced factor dosages or ITI may use bypassing agents or emicizumab. All available prophylaxis products can effectively prevent bleeding; however, each can have different patient responses, safety profiles (inhibitor development risks), costs, and product characteristics (half-life, effects on monitoring). The choice of prophylaxis product is made as a team evaluating the patient's specifics circumstances and needs. The goal of prophylaxis is to prevent bleeding at all times.

**Roctavian® (valoctocogene roxaparvovec-rvox)**

Clinical Trials:

*GENEr8-1 (NCT03370913)*

- Phase 3 prospective, open-label, single-dose, single-arm conducted with a median follow-up of 60.2 weeks (range, 51.1 to 150.4). All participants were male ages ≥18 years with severe hemophilia A (FVIII activity level ≤1 IU/dL) receiving FVIII prophylaxis ≥1 year before enrollment and treated/exposed to FVIII concentrates/ cryoprecipitate for ≥150 exposure days. Individuals were excluded if that had anti-AAV5 antibodies, chronic/active hepatitis B/C, HIV, current/prior FVIII inhibitor, significant liver dysfunction/fibrosis, cirrhosis, or liver function test abnormalities. At baseline 61.9% were receiving prophylaxis with standard half-life products, 27.6% with extended half-life products, and 17.9% plasma-derived products. No participants were receiving Hemlibra.
- All participants received valoctocogene at a dose of $6\times10^{13}$ vector genomes (vg) per kilogram of body weight through peripheral vein infusion. Glucocorticoids or other immunosuppressant (IS) were administered in response to ALT elevations. FVIII prophylaxis continued through 4 weeks after infusion; then as needed. The primary endpoint was the change from baseline in FVIII activity at 49-52 weeks after infusion. Baseline FVIII activity level imputed as 1 IU/dL (no FVIII washout period was required).
- Efficacy: In the mITT population (132 participants) the mean and median changes from baseline were 41.9 IU/dL (95% confidence interval [CI], 34.1 to 49.7; P<0.001) and 22.9 IU/dL (interquartile range, 10.9 to 61.3). At weeks 49-52, median FVIII activity level was ≥ 40 IU/dL (i.e., nonhemophilic) in 50 participants (37.9%), > 5 and < 40 IU/dL (mild hemophilia) in 66 participants (50.0%), and < 5 IU/dL in 16 participants (12.1%); 12 participants (9.1%) had a median FVIII activity level of < 3 IU/dL
- Most common adverse reactions (≥5%): nausea (31%), fatigue (16%), headache (7%), infusion-related reactions (7%), vomiting (6%), and abdominal pain (6%). The most common laboratory abnormalities (≥10%): elevated alanine transaminase (ALT) (81%), aspartate aminotransferase (AST) (69%), lactate dehydrogenase (LDH) (57%), creatine phosphokinase (CPK) (45%), FVIII activity levels (28%), gamma-glutamyl transferase (GGT) (18%), and bilirubin (13%) greater than the upper limit of normal (ULN). There were 6 serious ARs related to treatment: ALT elevation, presyncope, maculopapular rash, anaphylaxis, and hypersensitivity reaction.
    - 92/112 patients (82%) required corticosteroids for ≥1 episodes of ALT elevation, 39/112 (35%) required alternate IS.

*GENEr8-1 (NCT03370913):* Primary analysis of the change in the annualized treated bleeding rate at 2 or more years after gene transfer, an extension trial of GENEr8-1

- Participants were followed for 104 weeks after gene transfer. The primary endpoint (amended in response to FDA feedback) was the change in annualized treated bleeding rate in the rollover population, tested for noninferiority (margin, 3.5 episodes per year; estimated from pivotal studies of factor VIII replacement products), as compared with baseline. The efficacy evaluation period (EEP) started from study day 33 (week 5), or the end of FVIII prophylaxis including a washout period after gene therapy, whichever was later, and ended when a patient completed the study. Secondary endpoints included the change from baseline to week 104 in FVIII activity in the mITT population and change from baseline in annualized number of bleeding events at week 104 compared to baseline
- Efficacy: Among the rollover participants (N=112), the mean change in annualized treated bleeding rate was -4.1 bleeding events (95% CI, -5.3 to -2.9) per year (-84.5%, P<0.001). This change exceeded the noninferiority margin of 3.5.
    - Annualized occurrence of all bleeding events (ABR) during post prophylaxis period: In the published clinical trial the ABR changed from baseline in the rollover population by a mean of −4.1 (95% CI, −5.4 to −2.8) bleeding events per year (–77.0%, P<0.001). In the FDA approval letter, the mean imputed EEP ABR was 2.6 bleeds/year, compared to a mean observed baseline ABR of 5.4 bleeds/year, with a mean difference in ABR of -2.8 bleeds/year (95% confidence interval (CI): -4.3, -1.2). Of note, BioMarin did not input ABR when patients used prophylaxis treatment during the EEP. In the package insert, the FDA input an ABR of 35 for the periods when patients were on prophylaxis. This resulted in a calculated mean ABR reduction of 52%, as opposed to 77% in the published clinical trial.
    - FVIII activity increased from baseline (imputed at 1 IU per deciliter) to week 104 by a mean of 22.0 IU/dL (95% CI, 16.4 to 27.7; P<0.001) as measured with a chromogenic substrate assay (CSA) in the mITT population and by 35.1 IU/dL (95% CI, 26.9 to 43.2) as measured with a one-stage assay. Data for two participants who did not complete week 104 were imputed as 0 IU/dL.
    - The mean annualized FVIII concentrate consumption at baseline was 3961.2 ± 1751.5 IU/kg/year, compared to after treatment: 69.9 IU/kg/year. The change in mean was -3891.3 (95% CI, -4221.0 to -3561.5) (98.2% reduction; P<0.001).
    - 10/112 subjects returned to routine prophylaxis as of 3-year data cutoff. Per FDA analysis, a total of 22 subjects [20% (including 10 subjects who had returned to prophylaxis)] identified as having not ever having benefitted from valoctocogene (n=5), or for whom benefit was lost (n=17) over a median time of 2.3 (range: 1.0 to 3.3) years as of 3-year data

cutoff. In the directly enrolled population of 22 subjects, 1 subject did not respond (5%) and 6 subjects (27%) lost response to valoctocogene over a median time of 3.6 (range: 1.2 to 4.3) years as of the 3-year data cutoff.

- Most common nonlaboratory adverse reactions (incidence ≥5%): infusion-related reactions (including hypersensitivity reactions and anaphylaxis), nausea, headache, fatigue, vomiting, diarrhea, and abdominal pain. The most common laboratory adverse events (incidence ≥10%) were elevations > upper limit of normal (ULN) in ALT, aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactate dehydrogenase, gamma glutamyl transferase (GGT), bilirubin, and FVIII activity level. 5 subjects had 6 serious adverse events (SAEs) attributed to treatment: anaphylaxis, Grade 3 ALT elevation, and symptoms of hypersensitivity reaction. 97 subjects (87%; 97/112) in the rollover population received IS for ALT elevation. 92 (82%; 92/112) subjects received corticosteroids (prednisone or prednisolone), while 39 subjects (35%) received alternate IS that included tacrolimus and mycophenolate. The median (range) duration of overall IS, corticosteroid, and alternate IS use was 39.6 (3.4, 131), 35 (3.1, 120), and 26 (6, 118) weeks respectively. 20 subjects received > a year of IS therapy.

**Cost-effectiveness studies:**

Institute for Clinical and Economic Review (ICER): Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value[4]

**Hemgenix®:**

- Compared to factor IX prophylaxis, ICER concludes that there is moderate certainty of a small or substantial net health benefit, and high certainty of at least a small net health benefit (B+)
- At a price of $3,500,000, etranacogene transitions from being not cost effective at $150,000 per QALY to a dominant treatment at 7.5 years
- The Health Benefit Price Benchmark (HBPB) is $2.93 to $2.96 million
- Due to the high costs of factor prophylaxis, all patients could be treated with etranacogene without crossing the annual budget impact threshold

**Beqvez®**

- ICER evaluation has not been completed for this gene therapy.
- UK/NICE analysis is ongoing as of the publication of this policy.

**Roctavian®:**

- Low certainty about the net health benefit (I) for valoctocogene compared with emicizumab. Moderate certainty of a comparable, small, or substantial health benefit with high certainty of at least a comparable net health benefit (C++) for valoctocogene compared with factor VIII prophylaxis
- The Health Benefit Price Benchmark (HBPB) is $1.96 million
- Valoctocogene transitions from not being cost effective at $150,000 per QALY to being a dominant treatment in year four (cycle 8) at a placeholder price of $2,500,000.

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**Table 1**

| Brand Name | Generic Name | Adeno-Associated Virus (AAV) vector | HCPCS Code |
| --- | --- | --- | --- |
| Beqvez® | fidanacogene elaparvovec-dzkt | serotype Rh74var (AAVRh74var) | J1414 |
| Hemgenix® | etranacogene dezaparvovec-drlb | serotype 5 (AAV5) | J1411 |
| Roctavian® | valoctocogene roxaparvovec-rvox | serotype 5 (AAV5) | J1412 |