Healthy Blue

Medical Policy

Subject:	Gene Therapy for Hemophilia		
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Description/Scope

This document addresses gene therapy for hemophilia, a congenital medical condition in which the blood does not clot normally due to lack of sufficient blood-clotting proteins known as clotting factors. There are several forms of hemophilia, the most common of which are hemophilia A, which involves a deficiency in clotting factor VIII, and hemophilia B, which involves a deficiency in clotting factor IX. Gene therapy products for hemophilia use a virus vector with a working copy of the missing gene attached (factor VIII and factor IX for hemophilia A and B, respectively).

Position Statement

Medically Necessary:

A one-time infusion of etranacogene dezaparvovec-drlb is considered **medically necessary** in individuals who meet **all** of the following criteria:

A. Diagnosis of hemophilia B; **and**
B. Age 18 years or older; **and**
C. Base factor IX level is less than 1 international unit (IU)/deciliter (dL) (or 1% endogenous Factor IX); **and**
D. Poor disease control despite optimal management, including comprehensive care*, as manifested by *either* criterion 1 or 2:
    1. Individual is using routine prophylaxis factor replacement therapy; **and**
        i. Individual has documented history of *one of the following* while on routine prophylaxis factor replacement therapy:
            a. One or more episodes of spontaneous bleeding into joint; **or**
            b. One or more episodes of spontaneous bleeding into the central nervous system; **or**
            c. Four or more episodes of soft tissue bleeding in an 8-week period.

    or

    2. Individual is using on-demand therapy and has a documented history of at least 12 bleeding episodes over the previous year; **and**
E. No history of factor IX inhibitor; **and**
F. Absence of active infection; **and**
G. Absence of any immunosuppressive disorder; **and**
H. Absence of significant liver dysfunction or disease, defined as *at least one of the following*:
    1. Liver cirrhosis of any etiology; **or**
    2. Hepatitis B or C; **or**
    3. Alanine transaminase (ALT) at least 3 times the upper limit of normal; **or**
    4. Bilirubin at least 3 times the upper limit of normal; **or**
    5. Alkaline phosphatase at least 3 times the upper limit of normal; **or**

6. International normalized ratio (INR) at least 1.4.

Investigational and Not Medically Necessary:

Etranacogene dezaparvovec-drlb is considered **investigational and not medically necessary** when the criteria above are not met.

Use of all other gene replacement therapies to treat hemophilia is considered **investigational and not medically necessary**.

See discussion of comprehensive care in Background/Overview section, below.

Rationale

Hemophilia B

Etranocogene dezaparovec-drlb (Hemgenix®) (CSL Behring)

Etranacogene dezaparvovec-drlb, previously known as AMT-061, is the only gene therapy for hemophilia that has received approval from the Food and Drug Administration (FDA). It uses an adeno-associated virus serotype 5 (AAV5) vector that carries the Padua gene variant of Factor IX. Etranacogene dezaparvovec-drlb 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 repeated, serious spontaneous bleeding episodes.

In 2019, Von Drygalski and colleagues published data from a Phase IIb trial of 3 adults with moderate to severe hemophilia B (factor IX activity ≤ 2% per year) who received a single dose of etranocogene dezaparvovec-drlb (AMT-061). The trial aimed to collect preliminary data on the safety and efficacy of the 2×10^{13} genome copies (gc)/kilogram (kg) dose of the product prior to further study in the HOPE-B (Health Outcomes With Padua Gene; Evaluation in Hemophilia-B) phase III trial. At week 26, mean factor IX activity was 47% (range, 33% to 57%). There were no reported bleeds during the 26 weeks of follow-up and there were no reported serious adverse events (SAEs).

Von Drygalski and colleagues (2022) reported additional follow-up data from the Phase IIb trial, discussed above. Data were available for participants 1 and 2 at 3 years and participant 2 at 2.5 years. Factor IX activity at follow-up was over 40% (in the non-hemophilic range) for participants 1 and 2, and was 32.3% (in the mild hemophilic range) for participant 3. All 3 participants remained prophylaxis-free. Overall, participants had annualized bleeding rate of 0.22 and 2 of the 3 participants did not experience any bleeds. The publication reported 1 SAE that occurred in the first year after treatment; this was worsening avascular necrosis requiring hip surgery.

The ongoing Phase III clinical trial, HOPE-B (NCT03569891) is evaluating individuals with severe or moderately severe hemophilia B who received a single intravenous administration of gene therapy. Inclusion criteria include being male, at least 18 years old, having severe or moderately severe congenital hemophilia B, currently on factor IX prophylaxis and exposure to factor IX protein for at least the past 150 days. Key exclusion criteria include a history of factor IX inhibitors or a positive factor IX inhibitor test at screening, select liver screening laboratory test

values over 2 times the upper limit of normal or history of hepatitis B or C or active infection (given the risk of potential hepatotoxicity), a positive HIV test that is not controlled with anti-viral therapy, and previous gene therapy treatment. A total of 67 individuals were enrolled in the trial.

FDA approval in November 2022 was based on an 18-month interim analysis of data from the HOPE-B trial. A total of 54 of the 67 enrolled individuals were dosed with etranacogene dezaparvovec-drlb and were included in the analysis. The FDA product label (2022) reported efficacy data up to 18 months post treatment; 53 of the 54 dosed individuals completed the 18-month follow-up. The person who did not complete follow-up died at month 15 after dosing for reasons deemed unrelated to treatment. The primary efficacy outcome was a non-inferiority analysis of the annualized bleeding rate (ABR) from months 7 to 18 after treatment, and this was compared to the ABR during the initial lead-in period. Individuals were permitted to continue their prophylaxis treatment up to 6 months after being dosed with etranacogene dezaparvovec-drlb. The mean ABR during months 7 to 18 were 1.9 bleeds per year (95% confidence interval [CI], 1.0 to 3.4). During the lead-in period, the estimated mean ABR was 4.1 (95% CI, 3.2 to 5.4). The ratio of the ABR in months 7 to 18 post-treatment compared with during the lead-in period was 0.46 (95% CI, 0.26 to 0.81). Two participants were unable to stop routine prophylaxis after gene therapy treatment, and a third individual, who stopped prophylaxis at 6 months per study protocol, received it again during days 396 to 534. Limitations of this analysis include that the study was uncontrolled (no comparison with individuals on factor replacement therapy), conducted in a relatively small number of people and unable to confirm long-term durability of the etranacogene dezaparvovec-drlb, a one-time therapy (efficacy and safety information beyond 18 months is not available at this time). Moreover, in this analysis, not all individuals were able to stop prophylaxis after treatment and 1 of 54 individuals resumed prophylaxis use after stopping for approximately 6 months, suggesting variable efficacy and a possible waning effect of the treatment. Additional long-term data is needed to establish the durability of etranacogene dezaparvovec-drlb in reducing bleeding and long-term complications, particularly as compared to standard of care factor replacement therapy (including Factor IX preparations with longer half-lives).

In a safety analysis combining data from the 2 clinical studies (n=3 and n=54), no SAEs were reported. The most common adverse events were alanine aminotransferase (ALT) elevations (42%), aspartate aminotransferase (AST) elevations (42%), blood creatine kinase elevations (42%), infusion-related reactions (33%), headache (18%), flu-like symptoms (14%), fatigue (12%) and malaise (12%). In 1 individual with an infusion-related reaction, infusion was stopped and not resumed. Nine of the 24 individuals with ALT elevations were treated with corticosteroids for a mean duration of 81 days. Nineteen of the 24 individuals with ALT elevations also had AST elevations.

One study participant with preexisting risk factors for developing hepatic cancer developed hepatocellular carcinoma, which was assessed as not likely related to etranacogene dezaparvovec-drlb (based on vector integration site analyses and whole genome sequencing). As noted in FDA prescribing information: “the integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development.” Although AAV is a non-integrating vector, it can integrate into the nuclear genome in small amounts; the clinical significance and risk of malignancy in the long-term is not known.

Given ongoing unknowns related to the long-term durability and safety of etranacogene dezaparvovec-drlb, and the highly established and robust efficacy of prophylactic therapy in reducing bleeding and long-term complications of bleeding, consideration for treatment should be limited to individuals with poor disease control despite optimal management (in the absence of contraindications to therapy such as presence of factor IX inhibitor, active infection, immunosuppressive disorder or significant liver dysfunction or disease).

Giroctocogene fitelparvovec (SPK-9001) (Pfizer)

A Phase I/II trial (NCT02484092) of SPK-9001 (giroctocogene fitelparvovec) enrolled 15 males aged 18 and older with factor IX coagulant activity ≤ 2% of normal. Interim data reporting on 10 of the study participants who received a dose of 5E11 vector genome (vg)/kg were published by George and colleagues (2017a). The primary objective was to assess the safety of gene therapy. Exploratory efficacy endpoints included change from baseline in the ABR, consumption of favor IX replacement therapy and infusions. After a follow-up period ranging from 28-78 weeks, the ABR rate was significantly reduced from pre-infusion (mean rate: 11.1 events per year) to post-infusion (mean rate: 0.4 events per year). At follow-up, 8 of 10 participants (80%) did not use factor IX replacement therapy and 9 of 10 (90%) did not have any bleeds after gene therapy infusion. No SAEs were reported.

In addition to the trial discussed above, an ongoing Phase III clinical trial, NCT04370054, is recruiting approximately 63 adult males with moderately severe to severe hemophilia B. The primary study outcome is the total ABR over 15 months.

Verbrinacogene setparvovec (FLT180a) (Freeline Therapeutics)

Verbrinacogene setparvovec, also known as FLT180a, uses an AAVS3 synthetic capsid vector that carries a gain-of-function Padua gene variant (R338L) of Factor IX. Results of a Phase I/II study evaluating verbrinacogene setparvovec (the B-AMAZE study) were published by Chowdary and colleagues in 2022. The study included 10 males at least 18 years old with hemophilia B that was categorized as severe (factor IX level < 1%) or moderately severe (factor IX level, 1-2%) with a severe bleeding phenotype. Individuals with evidence of inhibitors to factor IX were not eligible to participate. None of the participants had evidence of AAVS3 neutralizing antibodies. Participants were treated with 1 of 4 doses of vector; 3.84E11 (n=2), 6.40E11 (n=2), 8.32E11 (n=4). or 1.23E12 (n=2). All 10 individuals completed the 26-week trial. In the total study population, the mean ABR at baseline was 2.93 events per year (range, 0 to 7.3) and was 0.71 events per year (range, 0 to 1.7) after treatment. Annualized factor IX consumption decreased from a mean at baseline of 226,026 IU per year to a mean of 9723 IU per year after receiving gene therapy. There were 12 SAEs that were thought to be related to gene therapy; 9 of these were an increase in liver aminotransferase levels.

Hemophilia A

Valoctocogene Roxaparvovec (Biomarin Pharmaceuticals)

Data from a phase I/II dose-escalation study evaluating valoctocogene roxaparvovec for hemophilia A (NCT02576795) have been published. The study included 15 males aged 18 and older with severe hemophilia A disease (base factor VIII level ≤ 1 IU/dL who had no history of factor VIII inhibitor development. Individuals who used on-demand therapy were required to have had ≥ 12 bleeding episodes in the previous 12 months. Individuals were excluded if they had detectable pre-existing immunity to the AAV5 capsid, evidence of active infection, any immunosuppressive disorder or any bleeding disorder other than hemophilia A, were HIV positive or had significant liver dysfunction. Study participants were required to discontinue using prophylactic factor VIII replacement therapy but were permitted to use factor VIII therapy if they experienced a bleeding episode during the study. Participants received a single intravenous injection of one of four doses of gene therapy: 6E12 vg/kg (n=1),

2E13 vg/kg (n=1), 6E13 vg/kg (n=7) or 4E13 (n=6). The primary aims of the study were to assess the number of participants with treatment-related adverse events over 5 years and to determine the dose of gene therapy needed to achieve expression of factor VIII ≥ 5% of normal activity (> 5 IU/dL) 16 weeks after infusion. Factor VIII activity levels were performed at a central laboratory and were measured in two ways; by a one-stage activated partial thromboplastin time-based clotting assay and a chromogenic factor Xa assay.

Individuals were sequentially enrolled in the study, with those enrolled first receiving the lowest dose of gene therapy. Rangarajan and colleagues (2017) reported 1-year data on the first three cohorts (n=9). In 6 of 7 individuals in the higher-dose cohort (6E13 vg/kg), factor VIII activity increased to a normal level (> 50 IU/dL) and this level was maintained at 1 year. In 6 individuals in the higher-dose cohort who had received factor VIII prophylaxis before trial entry, the median ABR decreased from 16 events per year to 1 event per year. One SAE, progression of chronic arthropathy, was reported.

Pasi and colleagues (2020) reported on all four cohorts (n=15) and up to 3 years of follow-up data. Three years after infusion, the 2 individuals in the lowest-dose cohorts (6E12 vg/kg, n=1 and 2E13 vg/kg, n=1), had factor VIII expression below IU/dL. Three-year data were also available for the 7 individuals in the third cohort, those who received the 6E13 vg/kg dose. At the end of years 1, 2 and 3, the mean factor VIII activity levels as measured by chromogenic assay were 64 IU/dL, 36 IU/dL and 33 IU/dL, respectively. Mean factor VIII values at the same time points using the one-stage assay were 104 IU/dL, 59 IU/dL and 52 IU/dL, respectively. After reaching a peak factor VIII level, the mean factor VIII expression decreased by 43% during year 2 and by 10% during year 3. In the third cohort, the mean annualized rate of bleeding events decreased by 96%, from a mean of 16.3 (standard deviation [SD), 15.7) events per year at baseline to a mean of 0.7 (SD, 1.6) events per year at the end of year 3. At baseline, only 1 of 6 participants who were receiving prophylaxis was free from breakthrough bleeding events. At the end of the third year of follow-up, 6 of 7 participants (86%) were free from bleeding events.

Two-year follow-up data were available on the 6 participants in the fourth cohort who received the highest dose of gene therapy, 4E13. The mean factor VIII activity level, according to the chromogenic assay, was 21.0 IU/dL at the end of year 1 and 15 IU/dL at the end of year 2. Mean factor VIII levels according to the one-stage assay were 31 IU/dL at the end of year 1 and 23 IU/dL at the end of year 2. In this cohort, Factor VIII level decreased by 30% during the second year after infusion. None of the individuals in the third or fourth cohorts were using prophylactic factor replacement at the end of year 3. In cohort 4, the annualized rate of bleeding events decreased by 92%, from a mean of 12.2 (SD, 5.4) events per year in the year before study entry to a mean of 1.2 (SD, 2.4) events per year at the end of year 2. All 6 individuals in cohort 4 were using prophylactic replacement therapy at baseline. In the year before study entry, 1 of these 6 individuals (17%) was free from breakthrough bleeding events. At the 2-year follow-up, 4 of 6 individuals (67%) were free from bleeding events.

All of the study participants had at least 1 adverse event. The most common AE was elevation of the alanine aminotransferase level with 14 events; 13 were grade 1 and 1 was a grade 2 event. The elevations in the alanine aminotransferase level were managed with glucocorticoid treatment. Three participants experienced SAEs at some point during the study. These included 1 case of grade 2 pyrexia, along with myalgia and headache that occurred within 24 hours of gene therapy infusion. Symptoms resolved within 48 hours. Two participants had SAEs associated with pre-existing hemophilic arthropathies; these were determined by investigators to be unrelated to treatment.

Data from a phase III trial (NCT03370913) evaluating a single 6E13 vg/kg dose of valoctocogene roxaparvovec were published in 2022 by Ozelo and colleagues. Eligibility included being at least 18 years old with severe congenital hemophilia A (factor VIII activity level ≤ 1 IU/dL), having received prophylaxis with factor VIII concentrates for at least 1 year prior to enrollment and being negative for factor VIII inhibitors. Key exclusion criteria were the presence of anti-AAV5 capsid antibodies, HIV infection, and substantial liver dysfunction, fibrosis or cirrhosis. The primary efficacy outcome was change from baseline in factor VIII activity at 1 year. A total of 181 men were screened, 144 were enrolled in the study and 134 were dosed with 6E13 vg/kg of valoctocogene roxaparvovec and completed the week 49-52 visit. Anti-AAV5 capsid antibodies were present in most (26 of 37) of the men who were ineligible after screening. Of the 134 individuals who received a dose of gene therapy, 132 were HIV-negative and were included in a modified intention-to-treat (ITT) population. In the modified ITT analysis, the mean change from baseline in the factor VIII activity level at 1 year was 41.9 IU (95% CI, 34.1 to 49.7) per deciliter. The median change was 22.9 IU per deciliter. There were 17 participants who had at least 2 years of follow-up. This group had mean factor VIII activity levels of 42.2 IU per deciliter at week 49-52 and 24.2 IU per deciliter at week 104. Median factor VIII activity levels in this group were 23.9 IU per deciliter at week 49-52 and 14.7 IU per deciliter at week 104. In the modified ITT population, the mean and median annualized rates of treated bleeding episodes were 4.8 per year and 2.8 per year, respectively, at baseline and 0.8 bleeds per year and 0 bleeds per year, respectively, after week 4. In terms of safety, all 134 participants had at least one adverse event; most were grade 1 or grade 2. A total of 22 participants (16.4%) reported any SAE; five SAEs were determined by the investigators to be related to the study drug. All of the SAEs resolved and there were no reported deaths and none of the participants withdrew due to adverse events or developed factor VIII inhibitors.

Mahlangu (2023) reported 2-year findings of the Phase III trial. After a median follow-up of 110.9 weeks (range 66 to 194 weeks), the mean change in the annualized bleeding rate, compared with baseline (when the participants were receiving prophylaxis), was -4.1 bleeding events per year (95% CI, -5.3 to -4.1). The annualized rate of factor VIII use decreased by 98.2% from baseline. The Factor VIII activity increased from baseline by a mean of 22.0 IU per deciliter (95% CI, 26.9 to 43.). Nine individuals had an adverse event in Year 2, none of which were SAEs.

SPK-8011 (Spark Therapeutics)

In 2021, George and colleagues published results of a Phase I/II dose escalation trial evaluating a single dose of SPK-8011. Participants received 1 of 4 doses of gene therapy, ranging rom a low dose of 5E11vg/kg to 2E12 vg/kg. Participants were males at least 18 years old with congenital hemophilia A and baseline factor VIII activity 2% or less of normal value, no history of factor VIII inhibitory antibodies and SPK200 neutralizing antibody titers of 1:5 or less. A total of 18 men met inclusion criteria and were dosed. At baseline, 13 of the 18 were receiving factor VIII prophylaxis and the others received factor VIII on demand. After a median efficacy follow-up of 33.4 months, the median annualized rate of bleeding events decreased from 8.5 (range, 0 to 43) before SPK-8011 administration to 0.3 events per year (range, 0 to 6.5) after administration. The annualized number of factor VIII administrations decreased from a median of 57.5 infusions (range, 24 to 245) per year at baseline to 0.6 (range, 0 to 28.6) after administration. One drug-related SAE was reported, elevated liver aminotransferase level.

An ongoing trial, NCT03432520, involves long-term follow-up of individuals with hemophilia A who have previously received SPK-8001 in a Spark-sponsored trial, with an estimated enrollment of 40 individuals.

A 2020 Cochrane review searched for and did not identify any randomized controlled trials (RCTs) or quasi-RCTs comparing gene therapy for hemophilia A or B to standard treatment or a different potentially curative treatment (such as stem cell transplant) (Sharma, 2020).

Background/Overview

Hemophilia is an inherited bleeding disorder that impairs the blood clotting process. The disease results in prolonged bleeding after an injury or surgery, easy bruising, and an increased risk of bleeding, including inside joints, muscles and/or the brain.

Hemophilia A, the most common type, involves a deficiency in blood clotting factor VIII and is caused by mutations in the F8 gene whereas hemophilia B (also called Christmas disease) involves a deficiency in factor IX and is caused by mutations in the F9 gene. The F8 and F9 genes provide instructions for making proteins called coagulation factor VIII and IX, respectively, which are necessary for the blood clotting process. Mutations in the F8 or F9 genes lead to reduction in the level of these coagulation factors, or production of abnormal versions of these proteins.

Both hemophilia A and B are x-linked recessive genetic disorders; that is, the genes associated with the conditions are located on the X-chromosome. Hemophilia more commonly affects males because they have only one copy of the X-chromosome. Females have two copies of the X-chromosome; when they have a single altered copy of the F8 or F9 gene, the mutation results in about half the normal level of coagulation factor VIII or IX, which is generally not sufficient to cause hemophilia. Most females (about 90%) with a single altered copy of the F8 or F9 gene are asymptomatic carriers who have a 50% chance of passing on the disease to their sons. It is possible for females to have two altered copies of the gene causing hemophilia, but this occurs very rarely (Genetics Home Reference, 2012; GeneReviews, 2017a and 2017b).

The age at diagnosis and severity of symptoms of hemophilia A and B depend on the level of factor VIII or IX clotting activity (GeneReviews, 2017a and 2017b). Severity is categorized as follows:

- **Severe hemophilia** (factor clotting activity level < 1%): Usually diagnosed within the first two years of life. Without prophylactic treatment with factor replacement, individuals with severe hemophilia A or B may average 2 to 5 spontaneous bleeds per month. Spontaneous bleeding can occur into the joints, can lead to joint destruction, as well as into the brain, a dangerous and life-threatening event. Delayed bleeding after trauma is also common in individuals with severe hemophilia. Bleeding can be massive or persist as continuous oozing for days or weeks.

- **Moderate hemophilia** (factor clotting activity level 1-5%): Usually diagnosed before age five to six years. These individuals rarely have spontaneous bleeding, but do have prolonged bleeding or delayed oozing after relatively minor trauma. Frequency of bleeding episodes varies but generally occur between once a month and once a year.

- **Mild hemophilia** (factor clotting activity level 5-40%): Mild disease is often not diagnosed until later in life, depending on the individual's exposure to surgical procedures or serious injury. Individuals with mild

hemophilia do not have spontaneous bleeding episodes. Abnormal bleeding occurs with surgery or tooth extractions. The frequency of bleeding varies from once a year to once every 10 years.

The prevalence of hemophilia B is about one-fifth that of hemophilia A. In the United States, the birth prevalence of hemophilia A is approximately 1 in 6500 live male births and the birth prevalence of hemophilia B is about 1 in 30,000 live male births (GeneReviews, 2017a and 2017b). For both hemophilia A and B, approximately 60% of individuals have severe disease, 15% have moderate disease and 25% have mild disease (National Hemophilia Foundation).

According to guidelines from the World Federation of Hemophilia (WFH) (2020), hemophilia is best managed in a comprehensive care setting. Comprehensive care is defined as care that "promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality". Comprehensive care involves a multidisciplinary team of healthcare professionals and, when available, uses accepted protocols and national treatment guidelines. The functions of a comprehensive care program are to provide or coordinate inpatient and outpatient care and services to individuals with hemophilia their families. Key tenets include:

- Patients should be seen by all core team members at least yearly (children every six months) for a complete hematologic, musculoskeletal, and psychosocial assessment and to develop, audit, and refine an individual's comprehensive management plan.
- To initiate, provide training for, and supervise home therapy with clotting factor concentrates where available.
- To educate patients, family members and other caregivers to ensure that the needs of the patient are met.
- To collect data on sites of bleeds, types and doses of treatment given, assessment of long-term outcomes (particularly with reference to musculoskeletal function), complications from treatment, and surgical procedures.

(Return to Position Statement)

The current medical management strategy for hemophilia is prevention and treatment of bleeding with infusions of replacement blood clotting factors. A variety of replacement products are available. All of the available prophylaxis products are considered effective, but may vary by patient response, safety profile (e.g., risk of inhibitor development), and product characteristic (e.g., product half-life, effects on monitoring). Prophylactic use of factor replacement therapy is recommended for individuals with severe hemophilia due to the high risk of spontaneous bleeding. Even a small increase in factor clotting activity can significantly reduce clinical bleeding rates. For moderate or mild hemophilia, recommendations regarding prophylactic use of factor replacement therapy are individualized depending on the person's clinical situation and preferences. Repeated intravenous infusions can be burdensome and involve risks such as infection from a central venous catheter. Other hemophilia management strategies include avoiding activities likely to cause trauma, exercising regularly to stimulate normal psychomotor development and improve fitness, practicing good oral hygiene and avoiding medications that increase bleeding risk.

Various gene therapy products for hemophilia A and hemophilia B are currently being investigated. These products use a virus vector with a working copy of the missing gene attached (factor VIII and factor IX for hemophilia A and B, respectively). The virus vector is the outer structure (capsid) of an adeno-associated virus (AAV) which is

incapable of replicating and thus unlikely to cause disease (Chuah 2013). The gene therapy is infused intravenously where it selectively targets hepatocytes (liver cells), the site where factor VIII and factor IX production primarily takes place. Several hemophilia B gene therapy products use AAVs that carry the Padua gene variant of Factor IX. The Padua variant is a naturally occurring missense mutation in the factor IX gene that increases its activity approximately 4- to 40-fold. This can potentially increase the efficacy of the treatment without using higher doses of vector (VandenDriessche, 2018) and may have implications for treatment durability. AAV vector-based gene therapy is intended to be a one-time treatment.

Pre-existing AAV neutralizing antibodies (NAbs) are a contraindication to receiving gene therapy as it is currently formulated, limiting the number of individuals potentially eligible for treatment. A review article identified found prevalences of anti-AAV NAbs ranging from 3% to 50% in individual studies (Louis Jeune, 2013). Pre-clinical studies have been conducted to evaluate gene therapy for inducing immune tolerance in individuals with hemophilia, but to date, clinical data are lacking (Arruda, 2016; Borsotti, 2018).

Some individuals with hemophilia may develop an inhibitor (an antibody directed against infused factor that inhibits the function of the factor). Individuals who develop inhibitors can often no longer use standard factor replacement to treat bleeding or to provide prophylaxis against bleeding. Individuals who have developed an inhibitor to factor have been excluded from gene therapy trials due to concerns about reduced efficacy.

There are a number of unanswered questions concerning gene therapy for hemophilia. It is unclear how certain characteristics, such as age at treatment, duration of disease and severity of disease, affect the likelihood that individuals with hemophilia would benefit from gene therapy. It is also unknown whether gene therapy for hemophilia will provide durable long- term benefit in individuals who initially benefit. Hepatocytes, the target of hemophilia gene therapy, have the capability to undergo cell division (Miyaoka, 2013). However, the scope and rate of hepatocellular turnover is variable, and in the context of gene therapy, it is unclear whether long-term liver regeneration will dilute the therapeutic effect of gene therapy (particularly in children, where ongoing proliferation of liver cells may dilute the number of viral genomes). Given this, current vectors are designed to target adult postmitotic hepatocytes (George, 2017b).

Long-term safety of gene therapy for hemophilia remains unknown. Theoretical safety concerns include inflammatory reaction to AAV proteins in other tissues or organs, unintended DNA insertion causing mutagenesis (i.e., possibility for cancer) or genotoxicity (cellular death), protein overexpression (causing for example, an amyloidosis-like condition), and virus transmission to other individuals including family, or into the environment. Insertional mutagenesis in reproductive cells could lead to infertility or, indirectly, to birth defects. In addition, use of the Padua variant of factor IX in hemophilia B gene therapy has uncertain safety issues; for example, a clinical trial evaluating verbrinacogene setparvovec found an SAE of arteriovenous fistula thrombosis in an individual with high factor IX levels after gene therapy using the Padua variant.

The FDA granted approval for etranacogene dezaparvovec-drlb (Hemgenix) in November 2022; this is the first FDA-approved gene therapy for hemophilia. According to the FDA:

> HEMGENIX is an adeno-associated virus vector-based gene therapy 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.

The product is approved for single-dose administration. The following warnings and precautions were included in the product label:

- Infusion reactions: Monitor during administration and for at least 3 hours after end of infusion. If symptoms occur, slow or interrupt administration. Re-start administration at a slower infusion once resolved.
- Hepatotoxicity: Closely monitor transaminase levels once per week for 3 months after HEMGENIX administration to mitigate the risk of potential hepatotoxicity. Continue to monitor transaminases in all patients who developed liver enzyme elevations until liver enzymes return to baseline. Consider corticosteroid treatment should elevations occur.
- Hepatocellular carcinogenicity: For patients with preexisting risk factors (e.g., cirrhosis, advanced hepatic fibrosis, hepatitis B or C, non-alcoholic fatty liver disease (NAFLD), chronic alcohol consumption, non-alcoholic steatohepatitis (NASH), and advanced age), perform regular (e.g., annual) liver ultrasound and alpha-fetoprotein testing following administration.
- Monitoring Laboratory tests: Monitor for Factor IX activity and Factor IX inhibitors.

Definitions

Adeno-associated virus (AAV): A small virus that infects humans and is not known to cause disease. Modified (non-replicating) AAVs are frequently used as viral vectors for gene therapy.

Comprehensive care: Coordinated delivery of care that "promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality", generally conducted by "a multidisciplinary team of healthcare professionals, in accordance with accepted protocols that are practical and national treatment guidelines, if available" (Srivastava, 2013). Comprehensive care represents optimal management of the severe form of hemophilia.

Gene replacement therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction.

Phenotype: Observable traits or characteristics in an individual that result from having particular genes (i.e., genotype) and from the interaction of the genotype with the environment.

X-linked recessive trait: A mutation in the gene on the X-chromosome. The phenotype is always expressed in males (who have only one X chromosome) and in females who have mutations in both of their X chromosomes.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

HCPCS

J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose (Hemgenix)

ICD-10 Diagnosis

D67	Hereditary factor IX deficiency

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

When services are also Investigational and Not Medically Necessary:
When the code describes any other gene therapy product for hemophilia.

HCPCS

	For the following unlisted codes **when specified as a gene therapy for hemophilia other than etranacogene dezaparvovec-drlb (Hemgenix):**
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. Arruda VR, Samelson-Jones BJ. Gene therapy for immune tolerance induction in hemophilia with inhibitors. J Thromb Haemost. 2016; 14(6):1121-1134.
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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/16/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections. Updated Coding section with 04/01/2023 HCPCS changes; added J1411 replacing NOC codes for Hemgenix.
New	12/01/2022	MPTAC review. Initial document development.
Preliminary Discussion	11/10/2022	MPTAC Pre-FDA Approval Review.
Preliminary Discussion	08/13/2020	MPTAC Pre-FDA Approval Review.