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OHSU Drug Effectiveness Review Project Summary Report – Gene Therapies for Hemophilia A and B (Feb 2023) Gene Therapies for Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia (Nov 2022)

Date of Review: October 2023

Date of Last Review: n/a
DERP Literature Search: Hemophilia A and B, database inception to 09/22/22
Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia, database inception to 07/26/22

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This is a summary of 2 different research reports from the Oregon Health and Science University Drug Effectiveness Review Project (DERP). The reports studied gene therapies which are Food and Drug Administration (FDA) approved for beta-thalassemia and hemophilia B. Gene therapies are currently being studied for 2 other conditions, sickle cell anemia and hemophilia A, but are not included in this report summary.
- Beta thalassemia is an inherited blood disorder where there is not enough hemoglobin made in the body, resulting in decreased production of healthy red blood cells (RBCs.) Hemophilia B is another inherited disorder that results in uncontrolled bleeding and mostly affects males assigned at birth.
- Gene therapies are a newer type of medication that usually involve getting just one dose. Most conditions being studied for gene therapy are uncommon. Studies for these treatments are often small and do not have a "placebo" group (a group that does not get the active therapy) to compare how safe and how well the drug works. This can make it difficult to understand how well these treatments work and what side effects they may have. We do not know how long the effect of gene therapies last.
- Betibeglogene autotemcel (ZYNTEGLO) is approved for adult and pediatric patients with beta-thalassemia who must have frequent red blood cell transfusions. Transfusions are when a person is given blood that came from a blood donor. Most patients who have received this gene therapy do not require as many red blood cell transfusions, and many no longer need red blood cell transfusions. We do not know if this improvement will last more than 2.5 years, but studies are happening now to answer this question. Many patients experienced adverse events when getting this treatment. Nearly every patient had mucositis (inflammation of mucosa such as the mouth), and it was significant in more than half of the patients. At least one in five patients had each of these: febrile neutropenia (fever in a person who has a low number of the blood cells that fight infections), vomiting, fever, hair loss, nose bleed, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder (changing of the

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color of skin), and itching. The most common severe adverse reactions were low counts of the different kinds of blood cells. This gene therapy requires treatment to destroy the bone marrow (inner part of the bone that includes stem cells and makes different kinds of blood cells) before it can be given. Patients must stay in the hospital for many weeks because they are at very high risk of bleeding and infections after getting this type of treatment.

- Etranacogene dezaparvovec (HEMGENIX) is approved for adult patients with severe forms of hemophilia B. Data show that patients who receive this therapy have fewer bleeding episodes each year than they did before receiving this therapy. Some patients no longer need to take other therapies to prevent bleeding such as the blood product known as Factor IX ("Factor 9"). We do not know if this improvement will last more than 18 months, but studies are happening now to answer this question. Some patients who received this medication had side effects, including reactions when the drug was being infused, and signs of damage to their liver. Some patients needed to take certain medications, called steroids, for many months while they had signs of inflammation in the liver after getting this medicine.
- Drug Use Research and Management (DURM) recommends that doctors who prescribe one of these medicines to a person enrolled in the Oregon Health Plan must show that certain criteria have been met to ensure the medicine is used safely and correctly before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the effectiveness of gene therapies for beta-thalassemia and hemophilia B?
2. What are the harms of gene therapies for beta-thalassemia and hemophilia B?
3. Are there any important subgroups of patients where these gene therapies have not been studied?

Conclusions:

Betibeglogene Autotemcel for Transfusion-Dependent Beta Thalassemia[1]

- Three non-controlled, open-label studies with 5 total publications for participants with transfusion dependent beta thalassemia (TDT) receiving betibeglogene were identified by DERP. The primary publications reported results for 45 total participants. Additional presentation abstracts provided quality of life (QoL) and long-term follow-up outcomes for participants enrolled in the primary studies. The studies were rated as having a *high* Risk of Bias (RoB) due to lack of a control group. All outcomes are rated very low certainty of evidence due to risk of bias, imprecision, and indirectness in 3 non-randomized studies. The primary efficacy endpoint of NORTHSTAR-2 was transfusion independence defined as a hemoglobin(Hb) of $\geq$ 9 g/dL starting 60 days after the last transfusion in patients who had not received RBC transfusions in 12 months or longer.
- Transfusion frequency was reduced and many patients achieved transfusion independence up to 29.5 months. NORTHSTAR-2 found transfusion independence was achieved in 91% (20 of 22) of patients with an average Hb level of 11.7 g/dL (range 9.5 to 12.8 g/dL), the two patients who did not achieve transfusion independence had a 67.4% and 22.7% reduction in transfusion volume.[1]
- Transfusion independence was achieved in 79.5% (35 of 44) of all evaluated patients in the combined study populations, and 3 of 9 (33%) of patients with the β^0/β^0 genotype. The β^0/β^0 genotype was excluded from NORTHSTAR-2.
- A high incidence of adverse events (AEs) occurred with betibeglogene, most often around the time of infusion. More than 20% of patients experienced each of the following at any severity: mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus.[2] Severe adverse events were common, including febrile neutropenia (51%) and mucositis (63%).[2] No deaths were reported.

Etranacogene dezaparvovec for Hemophilia B[3,4]

- Two non-controlled, open-label studies with 4 total publications in participants with hemophilia B were identified by DERP. The largest study was the phase 3, HOPE-B study which enrolled 54 participants with interim results reported via abstract. The full study was published after the DERP report was completed and was reviewed and graded by DURM. The second study, a phase 2b trial, enrolled 3 participants. Both are rated as having a *high* RoB and all conclusions are very low certainty of evidence due to high risk of bias and indirectness.
- Etranacogene reduced the annualized bleeding rate (ABR) in the phase 3 study from 4.19 (95% confidence interval [CI] 3.22 to 5.45) at baseline to 1.51 (95% CI 0.81 to 2.82) during months 7 to 18 post treatment vs. the 6 month baseline period ($P < 0.01$).
- Factor IX (FIX) replacement use decreased significantly by -248,825.0 IU (95% CI -291,149.9 to -206,500.1) during months 7 to 18 post treatment compared to the 6 month baseline period in the HOPE-B study ($P < 0.01$). Baseline unadjusted mean annualized exogenous factor IX consumption was 257,339±149,013 IU/year.
- Etranacogene administration resulted in improved FIX activity at 6 months (least-squares mean [LSM] 36.2%; 95% CI 31.4% to 41.0%) and 18 months (LSM 34.3%; 95% CI 29.5 to 39.1) after treatment.
- Elevations in liver enzymes was a common AE. Alanine aminotransferase (ALT) was elevated for 20% of patients and 17% of patients were given glucocorticoid treatment for weeks to months.

Recommendations:

- Designate betibeglogene autotemcel and etranacogene dezaparvovec as non-preferred on the preferred drug list (PDL)
- Apply prior authorization (PA) to ensure clinically appropriate utilization.

Summary of Prior Reviews and Current Policy

- Gene therapies are a relatively new type of medication. Many currently available agents fall under the Oncology Policy, and several others have drug-specific prior authorization criteria. These 2 therapies are being reviewed by the Pharmacy and Therapeutics (P & T) committee for the first time and are the first gene therapy agents available for beta-thalassemia and hemoglobin B.
- Gene therapies are extremely costly and some have been introduced with prices of several million dollars for a one-time treatment, in addition to costs for necessary supportive care.
- Gene therapies often target relatively rare or uncommon conditions which have a clear genetic cause. Consequently, many of the conditions disproportionately affect those of a specific race or sex. For example, hemophilia B is more common in males assigned at birth with XY chromosomes because it is X-linked. Beta-thalassemia most prevalent in Asia and in the Mediterranean basin.

Methods:
The November 2022 drug class report on Gene Therapies for Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia and the February 2023 drug class report on Gene Therapies for Hemophilia A and B by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon P & T Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:
Gene therapy is a developing field of therapeutics. The Food and Drug Administration (FDA) has approved a number of gene therapies for oncology and non-oncology uses.[5] Data from recent Drug Effectiveness Review Project (DERP) reports will be summarized for the recent approvals of betibeglogene autotemcel (ZYNTEGLO) for use in certain beta-thalassemia patients and etranacogene dezaparvovec-drlb (HEMGENIX) for specific hemophilia B patients.[1,3]

<u>Beta Thalassemia</u>
Beta thalassemia is an inherited, genetic blood disorder where there is insufficient production of β-hemoglobin (β+) or an absence of β-globin (β°), resulting in decreased production of healthy RBCs. This may result in anemia and based on the severity of phenotype, beta thalassemia can be labeled as transfusion dependent beta thalassemia (TDT) or transfusion nondependent. There are different genotypic forms of this disease. Individuals with severe forms of the disease can require regular transfusions of packed RBCs, which can result in iron overload and the need for concomitant iron chelation therapy.[1]

A complete blood count is generally required to diagnose beta thalassemia. It is most prevalent in Asia and the Mediterranean basin, but is estimated to have increased 7.5% over the last 50 years in the United States. Migration was considered as an important factor for this higher trend in beta thalassemia prevalence.[1] Global incidence of symptomatic disease is approximately 1 in 100,000 and can vary greatly geographically.[6]

Treatment options for TDT include splenectomy, hematopoietic stem cell transplant (HSCT), and FDA-approved drug therapies such as luspatercept. Donor matching, reduced survival rate for adults, and risk of graft versus host disease (GVHD) are concerns when HSCT is used to treat people with beta thalassemia.[1] While HSCT is potentially curative, it is generally most successful in younger children with an HLA-identical sibling donor.[7] The FDA approved the first gene therapy for beta thalassemia in the form of betibeglogene autotemcel in August 2022.[2] Other gene therapies are currently under investigation. Outcomes used when caring for patients with TDT or researching interventions include hemoglobin levels, frequency of transfusions, fatigue, and QoL.[1] There are no clear minimum clinically important differences (MCID) for these outcomes. An evaluation by the National Institute for Health and Excellence (NICE) discussing the methodological challenges in evaluating gene therapy products was published in 2021 and reviewed the initial NORTHSTAR results.[7] The NICE recommendation was that "betibeglogene autotemcel is not recommended, within its marketing authorisation, for treating TDT in patients aged ≥12 years who do not have a $beta^0/beta^0$ genotype, when HSCT is appropriate, but an HLA- matched related hematopoietic stem cell donor is not available".[8] The conditional EU and UK marketing authorization was for those with TDT who do not have the $beta^0/beta^0$ genotype and when HSCT would be appropriate but there is not suitable donor.[9] The manufacturer withdrew its marketing application from the Medicines and Healthcare products Regulatory Agency in 2021 and the European Medicines Agency in 2022.[10,11]

Efficacy

Betibeglogene Autotemcel (ZYNTEGLO) is an autologous hematopoietic stem cell-based gene therapy indicated for treatment of adult and pediatric patients with beta-thalassemia who require regular RBC transfusions.[2] Efficacy and safety were evaluated in 3 non-randomized, single arm studies. The β^0/β^0 genotype or the IVS1-110 mutation was found in 9 of 22 patients of patients in the NORTHSTAR trial (which is a pooled summary of 2 phase 1-2 studies), while the NORTHSTAR-2 trial excluded patients with the β^0/β^0 genotype.[1] The ongoing NORTHSTAR-3 Study does allow the β^0/β^0 genotype in its inclusion parameters.[1] Published studies (N=45 patients) are at high risk of bias due to lack of control group, and GRADE ratings for confidence of evidence in relevant outcomes is very low.[1] The phase 1/2 NORTHSTAR study focused on engraftment, while the phase 3 NORTHSTAR-2 study primary efficacy endpoint was transfusion independence defined as a Hb of $\geq$ 9 g/dL starting 60 days after the last transfusion in patients who had not received RBC transfusions in 12 months or longer.[1] The median age across trials was 13 years and most patients were Asian.[2] While one study allowed inclusion up to 50 years of age, the combined age ranges for those enrolled in the studies are 4 to 34 years. Those under 5 years had to meet a minimum weight threshold of 6 kg to reasonably provide the minimum number of cells for the product manufacturing process.[1] Patients in all studies required a history of transfusion of at least 100 mL/kg/year of packed RBCs in the 2 years before enrollment, or at least 8 transfusions of packed RBCs/year in the past 2 years for those 12 years in older.[1,7] NORTHSTAR-2 found transfusion independence was achieved in 91% (20 of 22) patients with an average Hb level of 11.7 g/dL (range 9.5 to 12.8 g/dL), the two patients who did not achieve transfusion independence had a 67.4% and 22.7% reduction in transfusion volume.[1] NORTHSTAR found transfusion independence in 68% (15 of 22) of patients with a median Hb level of 11.2 g/dL.[1] Of those with the β^0/β^0 genotype or the IVS1-110 mutation, 3 of 9 (33%) achieved transfusion independence.[1,7]

Harms

Overall survival during study follow-up was 100% in published studies. The most common adverse events experienced in at least 20% of patients were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus. Grade 3 or higher febrile neutropenia (51%) or mucositis (63%) were common.[2] Serious adverse events were experienced by 37% of patients. The most common serious adverse events were pyrexia, thrombocytopenia, liver veno-occlusive disease, febrile neutropenia, neutropenia, and stomatitis.[2] The median duration of hospitalization from conditioning though discharge (N=30) was 44 days (range 29 to 92 days).[1] No deaths were reported.[1] Study characteristics can be found in **Table 1** and complete demographics and results can be found in the full report.[1] The package insert states there is a potential risk for insertion oncogenesis after treatment and that patients should be monitored lifelong for hematologic malignancies with a complete blood count at months 6, 12, and then annually for at least 15 years, in addition to an integration site analysis at months 6, 12 and then as warrented.[2]

Table 1. Study Characteristics of Betibeglogene for Transfusion-Dependent Beta Thalassemia[1]

Author, Year Trial Number Trial Name	Participants	Treatment Protocol	Study Design	Follow-up	Risk of Bias
Thompson et al., 2018 HGB-204 NCT01745120 HGB-205 NCT02151526 NORTHSTAR	N = 22 n = 18, HGB-204 n = 4, HGB-205	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 1/2 study	26 months	High
Locatelli et al., 2022 HGB-207 NCT02906202 NORTHSTAR-2	N = 23	Single infusion of autologous CD34+ hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector Target Dose: at least 5.0 million CD34+ cells per kilogram of body weight	Single-arm, open label, phase 3 study	29.5 months	High
Kwiatkowski et al., 2021 Kulozik et al., 2021 HGB-207 NCT02906202 NORTHSTAR-2 HGB-212 NCT03207009 NORTHSTAR-3	N = 30	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, phase 3 studies	24 months	Not performed (conference abstract)
Yannaki et al., 2021 LTF-303 NCT02633943	N = 44	Single infusion of autologous hematopoietic stem cells transduced ex vivo with gamma-globin lentiviral vector	Single-arm, open label, long-term follow-up study	45.6 months	Not performed (conference abstract)

Hemophilia B

Hemophilia B is a recessive, X chromosome-linked bleeding disorder mainly affecting males assigned at birth. Hemophilia B represents a deficiency in factor IX (FIX) and affects 1 in 25,000 live male births. Females assigned at birth are more likely to experience mild or moderate hemophilia than severe hemophilia B. Bleeding most often occurs in large joints, leading to hemophilic arthropathy, which results in significant pain and physical disability. Physical activity can greatly increase the risk for weight-bearing joint bleeds, and many affected people with hemophilia avoid sports, exercise, and physical activities. Risk of bleeding associated with physical activity and frequent infusions of on-demand and prophylactic clotting factor concentrates (CFCs) contribute to the reduced QoL in individuals with hemophilia B. The severity of hemophilia B, defined by percent of normal clotting factor level, is detailed in **Table 2**. Factor IX activity of over 5% of normal is associated with a lower risk of spontaneous bleeding than those with moderate or severe hemophilia and is generally the target level for routine prophylactic therapy to prevent or reduce the incidence of spontaneous bleeds.[3]

Table 2. Hemophilia B Disease Severity by Factor IX Levels[3]

Percent of Normal Factor IX activity	Disease Severity
<1%	Severe
1-5%	Moderate
5-40%	Mild

The current standard of care for hemophilia B is regular administration of prophylactic CFCs or other hemostasis products to prevent bleeding. This prophylaxis is recommended prior to the age of 3 years to prevent both acute bleeds and the long-term development of hemarthroses and joint disease.[3] Many CFCs have a short half-life, leading to breakthrough bleeding as factor levels fall close to baseline between intravenous administration of FIX.[3] Newer formulations of CFCs with an increased half-life and the use of monoclonal antibodies allow for extended intervals between administrations.[3] Outcomes used when caring for patients and researching interventions for hemophilia B tend to include annualized bleeding rate (ABR), response to treatment (e.g., number of CFC infusions or dose required to resolve a bleed or time from last infusion to bleeding episode), need for other therapies, and quality of life. There are no clear MCIDs for these. The Haem-A-Qol is a common questionnaire used for assessment of health-related quality of life.[12] It has been validated in adult patients ≥ 17 years old with hemophilia.[12] Questions use a 5-point Likert-type frequency scale (1= never, 2=rarely, 3=sometime, 4=often, 5=all the time).[12] Higher total scores indicate more impairment and the maximum score is 100.[12] There are 10 different domains (e.g., physical health, sports & leisure, work & school) with varying numbers of items in each domain.[12]

Efficacy

Etranacogene dezaparvovec-drlb (HEMGENIX) is an adeno-associated virus vector-based gene therapy.[13] It is indicated for adults with hemophilia B who currently use FIX prophylaxis therapy; or have current or historical life threatening bleeding; or have repeated, serious spontaneous bleeding episodes.[13] It was evaluated in 2 non-randomized, single arm studies. HOPE-B study was a phase 3, open-label study, using intra-subject comparison as the control (n=54).[3,4] Patients had 18 months of post-treatment follow-up.[4] Patients were observed for FIX prophylaxis during the ≥ 6 month lead-in period (baseline) and had a 64% reduction in ABR (all bleeds, primary endpoint) from 4.19 (95% CI 3.22 to 5.45) at baseline to ABR 1.51 (95% CI 0.81 to 2.82; $P < 0.01$) during months 7 to 18 after etranacogene was administered.[4] The adjusted ABR ratio was 0.36 (95% CI 0.20 to 0.64), meeting predetermined criteria for non-inferiority (primary endpoint) and superiority (secondary endpoint) compared to lead-in period.[4] The mean FIX activity increase was 39.0 ± 18.7% (range 8.2 to 97.1%) at 6 months, most patients had <1% FIX activity at diagnosis. These were sustained at 12 and 18 months.[4] Baseline unadjusted mean annualized exogenous factor IX consumption was 257,339±149,013 IU/year. Factor IX annualized consumption decreased by 248,825.0 IU/year (95% CI -291,149.9 to -206,500.1).[4] Fifty-two of 54 participants

(96.3%) stopped prophylactic FIX infusions.[4] One non-responder received a subtherapeutic dose equivalent to approximately 10% of the intended dose, and the other non-responder was noted to have an adeno-associated virus serotype 5 (AAV5) neutralizing antibody titer of 3,212.[4] Clinical thresholds for this titer are unknown and being assessed with further research.[13] The Haem-A-QoL showed a total mean score of 25.56 compared with 20.06 in the lead-in and post-treatment periods, respectively, resulting in a 21.5% score improvement ($P < 0.01$).[3,4] The FDA noted that with the single-arm open label trial design that reliable assessments of patient-reported outcomes cannot be made and the information would not be in the label.[14] Study characteristics can be found in **Table 3** and complete demographics and results can be found in the published article.[3,4]

Von Drygalski and colleagues reported efficacy outcomes for etranacogene in 3 participants in the phase 2b study. All participants had a baseline FIX activity of less than 1%. Mean FIX activity increased to 31% at 6 weeks, 38% at 12 weeks, and 47% at 26 weeks. No bleeds or FIX administration was reported during the study period (26 weeks).

Table 3. Study Characteristics of Etranacogene for Hemophilia B[3,4]

Author, Year Trial Number Trial Name Risk of Bias	Participants	Treatment Protocol	Study Design	Follow-up	Risk of Bias
Miesbach et al., 2022 Pipe et al., 2022 Pipe et al., 2023 NCT03569891 HOPE-B	Men ≥ 18 years with FIX coagulant activity ≤ 2% who had received continuous prophylaxis for ≥ 2 months N = 54	2 x 10 vg/kg	Open-label, multicenter, non-randomized, phase 3 study	18 months	High
Von Drygalski et al., 2019 NCT03489291	Men ≥ 18 years with moderate to severe hemophilia B (FIX coagulant activity ≤ 2%) receiving either prophylactic FIX or on-demand FIX with ≥ 4 bleeds/year or chronic hemophilic arthropathy N = 3	2 x 10 vg/kg	Open-label, multicenter, non-randomized study	Interim assessment at 26 weeks published; planned 52 weeks; additional long-term follow-up assessments over 4 years	High
Abbreviations: FIX: factor IX; vg/kg: vector genomes per kilogram.					

Harms

The HOPE-B study includes safety information for etranacogene in 54 participants in the phase 3 study. There were 92 treatment-related adverse events (TRAEs) affecting 69% of participants.[3,4] Of these TRAEs, 74 (80.4%) were mild, 16 (17.4%) were moderate, and 2 (2%) were severe.[3,4] An increase in alanine aminotransferase (ALT) was noted in 9 participants (16.7%), all of whom received corticosteroid treatment (mean duration = 79 days ± 26.6, range 51 to 130 days) and maintained FIX expression.[3,4] Additional TRAEs include headache (n = 8; 14.8%), influenza-like illness (n = 7; 13%), infusion-related reaction (n = 7; 13%), AST increase (n = 5; 9.3%), increase in blood creatine phosphokinase (n = 4; 7.4%), fatigue (n =4; 7.4%), nausea (n = 4; 7.4%), and arthralgia (n = 3; 5.6%).[3,4] Two SAEs were reported, these included 1 death related to cardiogenic shock and 1 case of hepatocellular carcinoma, neither of which were determined to be related to etranacogene.[4] The follow-up time was 18 months. No patients developed FIX inhibitors.[4]

Von Drygalski and colleagues reported harm outcomes for etranacogene in 3 participants in the phase 2b study.[3] Two adverse events possibly related to etranacogene were reported in 1 participant, including a self-limited headache on day 1 and a mild increase in C-reactive protein on day 14, neither of which required intervention.[3] Changes in liver transaminase concentrations were not determined to be clinically significant. One participant required prednisone at 50 mg daily for 5 days at day 94 for bronchitis.[3] No serious adverse events (SAEs) were reported.[3] **Table 4** summarizes adverse events reported in the 2 trials.

Table 4. Adverse events from Etranacogene for Hemophilia B Studies[3,4]

Author, Year **Study Name** **Study Name**	**Adverse Events**	**Serious Adverse Events**
Miesbach et al., 2022 Pipe et al., 2022 Pipe et al., 2023 NCT 03569891 HOPE-B	• Alanine aminotransferase increase: n=9 (16.7%) • Headache: n=8 (14.8%) • Influenza-like illness: n=7 (13%) • Infusion-related reaction: n=7 (13%) • Aspartate aminotransferase increase: n=5 (9.3%) • Blood creatinine kinase increase: n=4 (7.4%) • Fatigue: n=4 (7.4%) • Nausea: n= 4 (7.4%) • Arthralgia: n=3 (5.6%)	• Death: n=1; cardiogenic shock unrelated to study treatment • Hepatocellular carcinoma: n=1; unrelated to study treatment
Von Drygalski et al., 2019 NCT03489291 Not applicable	• Headache: n=1 • Elevation in C-reactive protein: n=1	

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Appendix 1: Current Preferred Drug List

PDL unassigned

Generic	Brand	Route	Form	PDL
etranacogene dezaparvovec-drlb	HEMGENIX	IV	VIAL	
etranacogene dezaparvovec-drlb	HEMGENIX	IV	KIT	
betibeglogene autotemcel	ZYNTEGLO	IV	PLAST. BAG	

Betibeglogene Autotemcel

Goal(s):

- Approve Betibeglogene Autotemcel (ZYNTEGLO) for conditions supported by evidence of benefit

Length of Authorization:

- Once in a lifetime dose.

Requires PA:

- Betibeglogene Autotemcel (billed as pharmacy or physician administered claim)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documentation that the patient has never received another gene therapy for any diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does patient have confirmed Beta-thalassemia?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the genotype documented?	**Yes:** Go to #6 Genotype_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the patient transfusion dependent, defined as requiring in each of the past 2 years: • 100 mL/kg/year or more of packed red blood cells (any patient age) OR • 8 transfusions or more of packed red blood cells per year (patients 12 years and older)	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient 5 years old or older?	**Yes**: Go to #9	**No:** Go to #8
8. Does the patient weigh at least 6 kg?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have cirrhosis or advanced liver disease?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is there documentation that the patient does not have active or chronic infections of HIV, hepatitis B, or hepatitis C?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Does the prescriber attest that the patient's general health and comorbidities have been assessed and that the patient is expected to safely tolerate myeloablation?	**Yes**: Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Has the patient (and/or guardian, if applicable) been educated on the risk of insertional oncogenesis and need for lifelong monitoring (bloodwork) at least annually?	**Yes**: Go to #13.	**No**: Pass to RPh. Deny; medical appropriateness
13. Is the patient of childbearing potential OR capable of fathering a child?	**Yes:** Go to #14	**No:** Approve one lifetime dose.
14. Is the patient pregnant, actively trying to conceive, or trying to father a child?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #15

Approval Criteria		
15. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant or father a child during treatment and for at least 6 months after administration of the gene therapy?	**Yes:** Approve for one lifetime dose	

P&T/DUR Review: 10/23 (SF)
Implementation: 11/1/23

Etranacogene dezaparvovec

Goal(s):
- Approve Etranacogene dezaparvovec (HEMGENIX) for conditions supported by evidence of benefit

Length of Authorization:
- Once in a lifetime dose.

Requires PA:
- Etranacogene dezaparvovec (billed as pharmacy or physician administered claim)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is it the FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is there documentation that the patient has never received another gene therapy for any diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient require continuous routine factor IX prophylaxis?	**Yes**: Go to #7	**No:** Go to #5
5. Does the patient have a history of repeated, serious spontaneous bleeding OR current or historical life threatening hemorrhage?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Did these events occur during adherence to physician recommended and maximally adjusted factor IX therapy (including routine factor IX prophylaxis, if indicated) AND adherence to appropriate lifestyle precautions?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Send to Medical Director for review.
7. Does patient have congenital hemophilia B with: • Severe Factor IX deficiency (<1% plasma factor IX activity) OR • Moderately-Severe Factor IX deficiency (1 to 2% plasma factor IX activity) with a severe bleeding phenotype?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Send to Medical Director for review.
8. Is the patient 18 years or older?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there documentation that the patient does not have factor IX inhibitors by a test within the past 3 months? Note: If positive initial test, may retest, ideally within approximately 2 weeks of original test.	**Yes**: Go to #10 Test Date_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Has this patient had a liver health assessment including all of the following: AST, ALT, ALP, total bilirubin, hepatic ultrasound, elastography, and recent (previous 3 months) screening for hepatitis B and C?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Were all hepatic enzymes and hepatic radiological tests normal AND were hepatitis B and C screenings negative? Note: Enzyme elevations which are transient and mild (less than twice the upper limit of normal) may answer "Yes" to this question.	**Yes**: Go to #13	**No:** Go to #12
12. Has the patient been evaluated and cleared for gene therapy treatment by a gastroenterologist or hepatologist?	**Yes**: Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is there documentation that the patient is either: • HIV negative OR • HIV positive and controlled (CD4 count ≤ 200/μL)?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Has the provider discussed enrollment in a study to measure pre-existing anti-AAV5 neutralizing antibodies with patient? Note: study details and contact information in gene therapy package insert.[1]	**Yes:** Approve one lifetime dose.	**No:** Pass to RPh. Deny; medical appropriateness

1. Hemgenix (etranacogene dezaparvovec-drlb) package insert.uniQure, Inc Lexington, MA: https://www.fda.gov/media/163467/download. November 2022.

P&T/DUR Review: 10/23 (SF)
Implementation: 11/1/23