Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCHEM040.1224	**HEMATOLOGICAL AGENTS** **GENE THERAPIES FOR HEMOGLOBIN DISORDERS** See Table 1 for medications covered by policy
Effective Date: 2/1/2025	**Review/Revised Date**: 10/24 (MTW)
Original Effective Date: 09/24	**P&T Committee Meeting Date**: 06/24, 12/24
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:
Medicare Part B

POLICY CRITERIA:

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

REQUIRED MEDICAL INFORMATION:
For beta-thalassemia, Zynteglo® or Casgevy® may be approved when all the following criteria are met:

1. Documented diagnosis of beta-thalassemia confirmed by genetic testing
2. Patient has transfusion-dependent disease defined as one of the following:
    a. History of transfusions of at least 100 mL/kg/year of packed red blood cells (pRBCs)
    b. Eight or more transfusions of pRBCs per year in the two years preceding therapy
3. Patient is clinically stable and eligible to undergo the pre-conditioning regimen and infusion regimen
4. Patient does not have any of the following:
    a. Prior history of receiving a hematopoietic stem-cell transplant
    b. Prior history of receiving gene therapy for the requested indication
    c. Advanced liver disease (such as evidence of cirrhosis and/or persistent alanine aminotransferase, aspartate transferase or direct bilirubin values greater than three times the upper limit of normal)

For sickle cell disease, Casgevy® or Lyfgenia® may be approved when all the following criteria are met:

1. Patient has a confirmed diagnosis of sickle cell disease with one of the following genotypes: beta-S/beta-S, beta-S/beta-0, beta-S/beta+ (Note: Additional genotypes will be considered on a case-by-case basis based on disease severity). The diagnosis may be confirmed with genetic testing results or provider attestation of genotype.
2. Patient has experienced at least four vaso-occlusive events/crises (VOEs/VOCs) in the previous 24 months. A VOE/VOC is defined as an event requiring a visit to a medical facility for evaluation of acute pain, acute chest syndrome, acute splenic sequestration, acute hepatic sequestration, or priapism lasting greater than two hours.
3. Patient is clinically stable and able to undergo the pre-infusion myeloablative chemotherapy regimen and gene therapy infusion regimen based on the assessment of the requesting provider
4. Documentation patient meets one of the following:
    a. Patient has experienced therapeutic failure of hydroxyurea despite use of a maximally tolerated dose for at least six months. Examples of therapeutic failure include incidence of one VOE/VOC or need for blood transfusion.
    b. Patient has had an intolerance or contraindication to hydroxyurea
5. Patient does not have any of the following:
    a. Prior history of receiving a hematopoietic stem-cell transplant
    b. Prior history of receiving gene therapy for the requested indication
6. **For Lyfgenia®**, must meet both of the following in addition to the criteria above:
    a. The patient has a contraindication to Casgevy® (exagamglogene autotemcel)
    b. The patient does not have disease with more than two alpha-globin gene deletions

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
For Casgevy® and Lyfgenia®: May be approved for patients aged 12 years or older
For Zynteglo®: May be approved for patients aged four 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

PHARMACY PRIOR AUTHORIZATION/STEP THERAPY POLICY AND CRITERIA ORPTCHEM040	HEMATOLOGICAL AGENTS GENE THERAPIES FOR HEMOGLOBIN DISORDERS See Table 1 for medications covered by policy

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 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.

INTRODUCTION:

There are two FDA approved gene therapies for the treatment of transfusion dependent beta-thalassemia (TDT), betibeglogene autotemcel (beti-cel, Zynteglo®) and exagamglogene autotemcel (exa-cel, Casgevy®). Beti-cel is a lentiviral vector gene therapy which adds a modified beta-globin gene to autologous hematopoietic stem cells, which enables the production of a modified functional adult hemoglobin. Exa-cel is the first FDA approved gene therapy utilizing CRISPR/Cas9 technology and modifies BCL11A expression in autologous hematopoietic stem cells which increases fetal hemoglobin (γ-globin) production which in turn increases functional hemoglobin production.

There are also two FDA approved gene therapies for the treatment of sickle cell disease (SCD), exagamglogene autotemcel (exa-cel, Casgevy®) and lovotibeglogene autotemcel (lovo-cel, Lyfgenia®). Exa-cel works in sickle cell disease by increasing fetal hemoglobin concentrations which reduces hemoglobin S concentration and prevents sickling of red blood cells. Lovo-cel is a lentiviral vector gene therapy which adds a modified beta-globin gene which results in the production of HbA^{T87Q}, a functional hemoglobin that is 99.9% similar to wild-type hemoglobin. Increased HbA^{T87Q} concentration reduces hemoglobin S concentration and prevents sickling of red blood cells.

FDA APPROVED INDICATIONS:

Betibeglogene autotemcel (Zynteglo®) is indicated for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.

Exagamglogene autotemcel (Casgevy®) is indicated for the treatment of

- Transfusion-dependent beta-thalassemia (TDT) in adults and pediatric patients 12 years or older.
- Sickle cell disease (SCD) in patients 12 years and older with recurrent vaso-occlusive crises.

Lovotibeglogene autotemcel (Lyfgenia®) is indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events.
Limitations of Use

- Following treatment with Lyfgenia, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions.
- Lyfgenia has not been studied in patients with more than two α-globin gene deletions

POSITION STATEMENT:
For transfusion-dependent beta-thalassemia (TDT):

- Current standard of care is blood transfusions and iron chelation therapy to manage iron overload. In addition, luspatercept, an erythroid maturation agent, is approved to reduce the number of required transfusions and its efficacy is based on low quality evidence from one phase 3 trial that showed at least a 33% reduction in blood transfusions in adult patients receiving chronic blood transfusions.[2]
- Hematopoietic stem cell transplant (HSCT) is the only other available curative treatment for transfusion dependent β-thalassemia. HSCT requires a matched donor and carries its own risks such as mortality, graft failure/rejection, younger patients have better outcomes.[2]
- Moderate quality evidence based on two phase 3 trials (Northstar-2[3], Northstar-3[4]) and one long-term follow-up trial (LTF 303) that beti-cel may achieve transfusion independence in adult and pediatric patients with beta-thalassemia who require regular red blood cell transfusions.
    - Phase 3 trials and long-term results show up to 7 years of treatment effect with beti-cel; however, the true duration of response remains unclear.
    - Northstar-2 was conducted in 23 patients with beta-thalassemia requiring regular transfusions and with a non-β0/β0 genotype. Northstar-3 was conducted in 18 patients whom had β0 /β0 or non-β0 /β0 genotype. The trials enrolled patients 50 years of age and younger and they were required to be transfusion dependent which was defined as those who had received transfusions of ≥100 ml per kilogram of body weight of packed red cells per year or those who had ≥eight transfusions per year in the 2 years before enrollment. Key exclusion criteria included any evidence of

severe iron overload warranting exclusion, a known and available HLA-matched family donor, prior receipt of gene therapy, prior HSCT, and advanced liver disease.
    - Warnings and precautions associated with beti-cel include delayed platelet engraftment, risk of neutrophil engraftment failure, risk of insertional oncogenesis, drug interaction with anti-retroviral and hydroxyurea use, interference with serology testing.
    - Most common adverse reactions (≥ 20%): mucositis, febrile neutropenia, vomiting, pyrexia (fever), alopecia (hair loss), epistaxis (nosebleed), abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus (itch).
    - Overall, the safety profile is consistent with that of the mobilization and conditioning agents.
    - Thus far, there have been no reports of malignancies or cases of insertional oncogenesis. There were no deaths reported.
- Based on a single low-quality, single-arm, open-label study, 91.4% of TDT patients were transfusion independent for at least 12 consecutive months up to 45 months after exagamglogene autotemcel infusion (TDT Trial 2, CLIMB THAL-111, NCT 03655678).[20]
    - Interim analysis of the pivotal CLIMB THAL-111 trial included efficacy data from 35 of 59 enrolled patients.[14,20] A total of 52 patients received exa-cel and were included in the safety analysis.
    - The primary efficacy endpoint was the proportion of patients achieving transfusion independence for 12 consecutive months.[20]
    - Key inclusion criteria: Diagnosis of TDT, history of requiring ≥ 100 mL/kg/year or 10 units/year of RBC transfusions in the past 2 years, and patients had to be fit for autologous stem cell transplant.[20]
    - Key exclusion criteria: Available and willing matched bone marrow donor, prior allo-HSCT, sickle cell beta thalassemia variant.[20]
    - Warnings and precautions include the risk of off-target gene editing, neutrophil or platelet engraftment failure, and hypersensitivity reactions. It should be noted that no instances of off-target gene editing have been found thus far in clinical studies. There are no contraindications to exa-cel therapy.[20]
    - The most common grade 3 or 4 adverse events were neutropenia (100%), thrombocytopenia (100%), leukopenia (98%), anemia (92%), mucositis (71%), and febrile neutropenia (54%). These are consistent with and attributed to the busulfan conditioning regimen. There were no deaths reported in this study.

- Beti-cel and exa-cel have demonstrated similar efficacy and safety outcomes based on the available data.

Cost Effectiveness Studies:
Institute for Clinical and Economic Review. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value, Final Evidence Report.[8]

- Compared to standard of care treatments (e.g. blood transfusion and iron chelation) beti-cel demonstrates at least an incremental net benefit compared to standard of care (B+).
- The cost-effectiveness threshold for beti-cel is $1.57 million ($150K/QALY)

For sickle cell disease (SCD):

- Based on a National Institutes of Health 2014 report, the current standard of care for sickle cell disease is to offer hydroxyurea therapy to any patient aged 9 months or older.[16] It is strongly recommended to start hydroxyurea therapy in patients who have experienced three or more moderate-to-severe pain crises in the past 12 months, patients with significant SCD related pain that affects their daily activities, patients who have severe/recurrent acute coronary syndrome (ACS), patients with symptomatic chronic anemia, and in adults and children with CKD who are erythropoietin.
- Per the American Society of Hematology (ASH), based on low quality evidence allogenic stem cell transplant should be offered to patients with an HLA-matched available donor who: have had a stroke or abnormal transcranial Doppler ultrasound, have frequent pain, or who have recurrent episodes of ACS.[15] In patients with an indication for transplant, transplantation at an earlier age has demonstrated better outcomes.
- Other FDA-approved therapies for sickle cell disease include: voxelotor, crizanlizumab-tmca, and L-glutamine. Updated guidelines have not been published to establish the place in therapy of any of these agents.
- Based on a single low-quality, single-arm, open-label study, 93.5% of SCD patients were free of VOCs for at least 12 consecutive months up to two years after exagamglogene autotemcel infusion. There were no cases of graft failure or rejection.[21]
    - Interim analysis of the pivotal CLIMB SCD-121 trial included efficacy data from 31 of 63 enrolled patients.[14,21] A total of 44 patients received exa-cel and were included in the safety analysis.
    - The primary efficacy endpoint was the proportion of patients who had not experienced a severe vaso-occlusive crisis (VOC) for at least 12 consecutive months.[21]

- Key inclusion criteria: Diagnosis of severe sickle cell disease, ≥ 2 VOC events during the past two years, no marrow donor available, and fit for autologous stem cell transplant.[21] Of note, only beta-S/beta-S, beta-S/beta-0, and beta-S/beta+ genotypes were represented in this trial.
- Key exclusion criteria: Available and willing matched bone marrow donor and >10 hospitalizations/ED visits related to non-SCD chronic pain.[21]
- Warnings and precautions include the risk of off-target gene editing, neutrophil or platelet engraftment failure, and hypersensitivity reactions. It should be noted that no instances of off-target gene editing have been found thus far in clinical studies. There are no contraindications to exa-cel therapy.[21]
- The most common grade 3 or 4 adverse events were neutropenia (100%), thrombocytopenia (100%), leukopenia (98%), anemia (84%), mucositis (86%), and febrile neutropenia (48%). These are consistent with and attributed to the busulfan conditioning regimen. There were no deaths reported in this study.

- Based on a single low-quality, single-arm, open-label study 88.2% of sickle cell disease patients (28/32 patients) were free of vaso-occlusive events between 6 and 18 months after infusion of lovotibeglogene autotemcel (95% CI 71-97). Ninety-four percent (30/32 patients) were free from severe VOE's that required hospitalization or multiple visits to an emergency department over a 72-hour period in the same follow up time (95% CI 79-99).
  - Interim analysis of Group C from the pivotal HGB-206 trial (NCT 02140554) which included efficacy data from 32 of 36 enrolled patients.[14, 22] A total of 35 patients received lovo-cel and were included in the safety analysis.
  - The primary efficacy endpoints were the proportion of patients who had complete resolution of all vaso-occlusive events (VOE-CR) and those who had resolution of severe vaso-occlusive events (sVOE-CR) measured between 6 and 18 months after lovo-cel infusion.[22]
  - Key inclusion criteria: Age 12-50, diagnosis of severe sickle cell disease with beta-S/beta-S, beta-S/beta-0, or beta-S/beta+ genotype, previous failure of hydroxyurea, at least 4 VOC events in the past two years, and no marrow donor available and fit for stem cell transplant.[22]
  - Key exclusion criteria: Available and willing matched bone marrow donor, HIV infection, active hepatitis B, hepatitis C, history of stroke or advanced liver disease, and prior receipt of allogeneic transplant.[22]
  - Warnings and precautions include increased risk of hematologic malignancies (e.g. acute myeloid leukemia and myelodysplastic syndrome), insertional oncogenesis, neutrophil or platelet engraftment failure, and hypersensitivity reactions.

  - The most common grade 3 or 4 adverse events were neutropenia (60%), thrombocytopenia (69%), anemia (33%), stomatitis (71%), and febrile neutropenia (44%). These are consistent with and attributed to the busulfan conditioning regimen.
  - There were three deaths reported in HGB-206. Two deaths were due to acute myeloid leukemia that developed after lovo-cel infusion in Group A. The manufacturing and conditioning processes were modified in groups B and C and no further therapy related deaths were reported. The third death was due to sudden cardiac death due to underlying disease and deemed to be not attributed to lovo-cel therapy.
- Exa-cel and lovo-cel have demonstrated similar efficacy, based on interim analyses of pivotal trials.
- Lovo-cel is associated with the development of hematologic malignancies and death in a small number of patients; however, full data from the pivotal trial is not yet available for analysis. Long-term study is needed to monitor for safety signals in a larger treatment population for both lovo-cel and exa-cel.

Cost-effectiveness studies:
Institute for Clinical and Economic Review (ICER): Sickle Cell Disease.[17]
- Compared to standard of care treatments (e.g. hydroxyurea, chronic blood transfusions, pain medication, iron chelation… etc.) exa-cel has a moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit (C++).
- Compared to standard of care treatments lovo-cel demonstrates at least an incremental net benefit compared to standard of care (B+).
- The cost-effectiveness thresholds for pricing of gene therapies for sickle cell disease are: $1.7 million ($150K/QALY) and $2.04 million ($200K/QALY).

United Kingdom National Institute for Health and Care Excellence (NICE): Draft guidance consultation – exagamglogene autotemcel.[18]
- Exa-cel is not recommended for routine or managed use as the acceptable cost effectiveness estimate is higher than what NICE normally considers a cost-effective use of NHS resources.

Table 1

Brand Name	Generic Name	HCPCS Code
Casgevy®	exagamglogene autotemcel	C9399 (NOC), J3590 (NOC)
Lyfgenia®	lovotibeglogene autotemcel	J3394
Zynteglo®	betibeglogene autotemcel	J3393

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