

<p>SUBJECT: CLINICAL POLICIES – GENE-EDITING THERAPIES FOR SICKLE CELL DISEASE And BETA THALASSEMIA</p> <p>POLICY NUMBER: HS-CP-MA I3w</p> <p>EFFECTIVE DATE: June 25, 2025</p> <p>SERVICE/PRODUCT LINE: MEDICARE – MEDICAL</p>	<p>Product Line (check all that apply):</p> <p><input type="checkbox"/> All</p> <p><input type="checkbox"/> Group HMO</p> <p><input type="checkbox"/> Individual HMO</p> <p><input type="checkbox"/> PPO</p> <p><input type="checkbox"/> POS</p> <p><input checked="" type="checkbox"/> Medicare</p> <p><input type="checkbox"/> FEHB</p>
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These guidelines are used in conjunction with the independent judgment of a qualified licensed physician and do not constitute the practice of medicine or medical advice. This Clinical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of members. This Clinical Policy is not intended to recommend treatment for members. Members should consult with their treating provider in connection with diagnosis and treatment decisions.

When coverage criteria are not fully established by Medicare including but not limited to National Coverage Decisions (NCD), Local Coverage Decisions (LCD), Medicare Manuals and National Coverage Articles, Sharp Health Plan develops Clinical Policies that serve as recommendations for medical necessity decisions. Sharp Health Plan utilizes evidence-based guidelines from nationally recognized professional organizations, peer reviewed medical and scientific literature and evidence-based consensus statements, which are all based on generally accepted standards of care.

- I. **BENEFIT STATEMENT:** Any service reviewed and approved by this Sharp Health Plan Clinical Policy must be a covered benefit according to the member’s evidence of coverage (EOC). Since benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in this clinical policy, decisions are subject to all terms and conditions of the applicable benefit plan. Benefit determinations should be based in all cases on the member’s contract benefits in effect at the time of service.
 - A. All reviewers must first identify member eligibility, and all decisions of this clinical policy are subject to current state and/or federal law. This Clinical policy does not constitute plan authorization, nor is it an explanation of benefits. In the event of a conflict, a member’s benefit plan, EOC, always supersedes the information in the Clinical Policies.
 - B. Sharp Health Plan provides coverage of, by furnishing, arranging for, or making payment for, all services that are covered by Part A and Part B of Medicare (if the enrollee is entitled to benefits under both parts) or by Medicare Part B (if entitled only under Part B) and that are available to beneficiaries residing in the plan’s service area.
 - C. Sharp Health Plan complies with CMS’s national coverage determinations and general coverage and benefit conditions included in Traditional Medicare laws, unless superseded by laws applicable to MA plans. This includes criteria for determining whether an item or service is a benefit available under Traditional Medicare.

II. REGULATORY: n/a**III. DESCRIPTION**

- A. This clinical policy should be utilized referencing the member's specific Member Handbook to confirm the member's coverage benefit(s).
- B. This policy defines the Sharp Health Plan (Plan) requirements for determination of medical necessity in order for to be covered.
- C. This policy is to be used when there is no CMS criteria (NCD,LCD, NCA, Medicare Manual) for the drug in question.
- D. This policy defines the Sharp Health Plan (Plan) criteria for coverage of medications with a parenteral (IM, SQ, IV, Intrathecal) route of administration. These are also referred to as a "medical benefit" medication. A separate policy governs medications administered through the pharmacy benefit (Sharp Health Plan Pharmacy Procedure for Formulary and Pharmaceutical Management Procedures Development
- E. Sickle cell disease is a genetic disorder caused by mutations in the hemoglobin β subunit gene. The mutations cause formation of an abnormal version of hemoglobin that causes deformation ("sickling") of red blood cells under certain conditions. The deformed cells can obstruct small blood vessels, resulting in pain, disability, and organ damage.
- F. Beta thalassemia is a genetic disorder caused by mutations in the hemoglobin β subunit gene that lead to reduced or absent production of β -globin. The resulting excess of α -globin inhibits formation of red blood cells and leads to increased hemolysis.
- G. Exagamglogene autotemcelis (Casgevy) consists of autologous CD34+ hematopoietic cells edited by CRISPR to reduce expression of BCL11A. After myeloablative conditioning, the edited cells are infused and engraft in the bone marrow. The resulting cell lineage has increased production of fetal hemoglobin (hemoglobin F) and γ -globin. In sickle cell disease, the increase in fetal hemoglobin reduces the concentration of hemoglobin S and consequently reduces or prevents the formation of sickle cells. In beta thalassemia, the increase in γ -globin reduces the excess of α -globin and improves the rate of formation and stability of red blood cells.
- H. Lovotibeglogene autotemcel (Lyfgenia) consists of autologous CD34+ hematopoietic cells edited by a lentiviral vector to produce hemoglobin A. After myeloablative conditioning, the edited cells are infused and engraft in the bone marrow. The resulting red blood cells have a lower concentration of hemoglobin S and are less likely to sickle.
- I. Betibeglogene autotemcel (Zynteglo) consists of autologous CD34+ hematopoietic cells edited by a lentiviral vector to add a functional β -globin gene. After myeloablative conditioning, the edited cells are infused and engraft in the bone marrow. The red blood cells produced by the edited precursors are able to produce functional adult hemoglobin.

IV. DEFINITIONS

- A. A Qualified Individual is a Sharp Health Plan (Plan) member.
- B. Experimental and Investigational drugs and devices:
 - 1. Considered experimental if the FDA has not issued a specific indication or NDC number for the

- specific drug or device AND they are currently under investigation in a registered Clinical Trial.
2. The Off-Label Use of an FDA approved prescription drug or device is not considered an experimental/investigational service if this off-label use is not currently being investigated in a registered Clinical Trial.
- C. Biosimilars: A biosimilar is a biologic that is highly similar to, and has no clinically meaningful differences from, another biologic that is already approved by the FDA (known as the original biologic or reference product). Biosimilars are made with the same types of natural sources as the original medication they were compared to; they are given the same way, have the same strength and dosage, and have the same potential side effects. A biosimilar provides the same treatment benefits as the original biologic.
- D. Injection: The introduction of a medicinal substance into the body; either subcutaneous, intramuscular, intravenous, intra-arterial or into other canals or cavities of the body. For purposes of this medical policy, a medication is provided either by a member (self-injectable) or by a medical provider. It is a "shot" or a dosage of medication given by way of a syringe and needle rather than over a period of time, though not to be given as part of a procedure.
- E. Infusion: The slow diagnostic, prophylactic, or therapeutic introduction of fluid or medicinal substance into a vein or tissue given over a period of time.

V. MEDICAL NECESSITY

- A. To be eligible for coverage under this policy, the member must be a Qualified Individual with active Plan membership; AND
- B. Member is being treated by or in consultation with a contracted hematologist; AND
- C. The provision of physician samples does not guarantee coverage; AND
- D. SICKLE CELL DISEASE INITIAL CRITERIA: either exagamglogene autotemcelis (Casgevy) or lovotibeglogene autotemcel (Lyfgenia) is considered medically necessary for members who meet all of the following criteria for an initial authorization:
 1. Member is at least 12 years of age; AND
 2. Member has sickle cell disease and both of the following:
 - a) $\beta S/\beta S$, $\beta S/\beta 0$, or $\beta S/\beta +$ genotype; AND
 - b) At least 4 severe vaso-occlusive events in the past two years; AND
 3. Previous trial and failure of hydroxyurea; AND
 4. History of at least 24 months of active treatment for sickle cell disease; AND
 5. Member is eligible for allogeneic stem cell transplant, but no HLA-matched donor is available; AND
 6. None of the following:
 - a) Clinically significant viral (including HIV, HBV, HCV), bacterial, fungal, or parasitic infection; OR

- b) Malignancy or myeloproliferative disorder; OR
 - c) Prior gene therapy; OR
 - d) Prior allogeneic transplant; OR
 - e) Prior gene therapy; OR
 - f) Current pregnancy or breastfeeding
- E. BETA THALASSEMIA INITIAL CRITERIA: Either exagamglogene autotemcelis (Casgevy) or Betibeglogene autotemcel (Zynteglo) is considered medically necessary for members who meet all of the following criteria for an initial authorization:
- 1. Member is at least 12 years of age (Casgevy) or at least 4 years of age (Zynteglo); AND
 - 2. Member has transfusion-dependent beta thalassemia and both of the following:
 - a) β^0/β^0 or non- β^0/β^0 genotype; AND
 - b) At least 100ml/kg of pRBCs per year or at least 8 transfusion events of pRBCs per year in the previous 2 years; AND
 - 3. Member is eligible for allogeneic stem cell transplant, but no HLA-matched donor is available; AND
 - 4. None of the following:
 - a) Clinically significant viral (including HIV, HBV, HCV), bacterial, fungal, or parasitic infection; OR
 - b) Malignancy or myeloproliferative disorder; OR
 - c) Prior gene therapy; OR
 - d) Prior allogeneic transplant; OR
 - e) Prior gene therapy; OR
 - f) Current pregnancy or breastfeeding

VI. NOT MEDICALLY NECESSARY

- A. The Plan is not required to cover services or benefits that are not otherwise covered under the terms and conditions of the Plan contract.
- B. Casgevy, Lyfgenia, and Zynteglo are considered not medically necessary when any of the above criteria have not been met.
- C. Repeat courses of Casgevy, Lyfgenia, and Zynteglo are not medically necessary.

VII. PROCEDURE/ATTACHMENTS

- A. Review and confirm the member's coverage benefit for the member's specific member

VIII. CODES: N/A

IX. REFERENCES

- A. Casgevy [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated, January 2024.
- B. Lyfgenia [package insert]. Somerville, MA: bluebird bio, Inc, December 2023.
- C. Zytiglo [package insert] bluebird bio, August 2022.
- D. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β -thalassemia. N Engl J Med. 2021;384(3):252-260.
- E. Kanter J, Walters MC, Krishnamurti L. Biologic, and clinical efficacy of LentiGlobin for sickle cell disease. N Engl J Med. 2022;386(7):617-628.
- F. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. Blood Adv. 2021;5(18):3668-3689.
- G. Institute for Clinical and Economic Review. Exa-cel and lovo-cel: final policy recommendations. Final report. August 21, 2023.

X. REVISION HISTORY

Date	Modification (Original, Reviewed or Revised)
6/5/25	Original

<p>Approved by: (Signature of VP /CMO)</p> 	<p>Approval date: 6/25/25</p>
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