Clinical Policy: Exagamglogene Autotemcel (Casgevy)

Reference Number: CP.PHAR.603
Effective Date: 12.08.23
Last Review Date: 02.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Exagamglogene autotemcel (Casgevy™) is an autologous CD34+ hematopoietic stem and progenitor cell-based therapy.

FDA Approved Indication(s)

Casgevy is indicated for the treatment of patients aged 12 years and older with:

- Sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs)
- Transfusion-dependent β-thalassemia (TDT)

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results, or other clinical information) supporting that member has met all approval criteria.

All requests reviewed under this policy **require Precision Drug Action Committee (PDAC) Utilization Management Review**. Refer to CC.PHAR.21 for process details.

It is the policy of health plans affiliated with Centene Corporation® that Casgevy is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Sickle Cell Disease (must meet all)**:**

1. Diagnosis of SCD with genetic confirmation of one of the following genotypes (a or b):
   a. β^S/β^S;
   b. β^S/β^0;
2. Prescribed by or in consultation with a hematologist and transplant specialist;
3. Age ≥ 12 years;
4. Documentation of ≥ 2 severe VOCs per year during the previous two years, with a severe VOC defined as one of the following (a, b, c, d, or e):
   a. An acute pain event that requires a visit to a medical facility and administration of pain medications (e.g., opioids or intravenous non-steroidal anti-inflammatory drugs [NSAIDS]) or packed red blood cell (pRBC) transfusions;
   b. Acute chest syndrome (ACS);
   c. Priapism lasting > 2 hours and requiring a visit to a medical facility;
   d. Splenic sequestration;
   e. Hepatic sequestration;

5. Failure of hydroxyurea at up to the maximally indicated dose for ≥ 6 months, unless contraindicated or clinically significant adverse effects are experienced* (*see Appendix D*);
   **Myelosuppression and hydroxyurea treatment failure: Myelosuppression is dose-dependent and reversible and does not qualify for treatment failure. NHLBI guidelines recommend a 6-month trial on the maximum tolerated dose prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. A lack of increase in mean corpuscular volume (MCV) and/or fetal hemoglobin (HbF) levels is not indication to discontinue therapy.*
6. Attestation from transplant specialist for both of the following (a and b):
   a. Member understands the risk and benefits of alternative therapeutic options such as allogenic hematopoietic stem cell transplantation (HSCT);
   b. Member is clinically stable and eligible to undergo myeloablative conditioning and HSCT;
7. Member has not received prior allogeneic HSCT;
8. Member has not received prior gene therapy;
9. Documentation from within the last 6 months that the member is negative for the presence of the following active infections: HIV, hepatitis B virus, and hepatitis C virus;
10. Member does not have advanced liver disease (*see Appendix E*);
11. Member does not have current malignancy or immunodeficiency disorder;
12. Documentation of member's body weight in kg;
13. Dose contains a minimum of 3 x 10^6 $CD34^+$ cells/kg.

Approval duration: 6 months (one-time infusion per lifetime)

B. Transfusion-Dependent β-Thalassemia (must meet all)**:**

1. Diagnosis of TDT with genetic confirmation (*see Appendix F*);
2. Prescribed by or in consultation with a hematologist and transplant specialist;
3. Age ≥ 12 years;
4. Documentation of one of the following (a or b):
   a. Receipt of ≥ 100 mL/kg or 10 units of pRBC per year for the previous two years (*see Appendix D*);
   b. Receipt of ≥ 8 transfusions of pRBC per year for the previous two years (*see Appendix D*);
5. Attestation from transplant specialist for both of the following (a and b):
   a. Member understands the risk and benefits of alternative therapeutic options such as allogenic HSCT;
   b. Member is clinically stable and eligible to undergo myeloablative conditioning and HSCT;
6. Member does not have any of the following (a, b, and c):
   a. Associated α-thalassemia and > 1 alpha chain deletion;
   b. Alpha multiplications;
   c. Associated sickle cell β-thalassemia;*
   **Sickle cell β-thalassemia is a type of SCD and should be evaluated under the SCD criteria (I.A)*
7. Member has not received prior allogenic HSCT;
8. Member has not received prior gene therapy;

9. Documentation from within the last 6 months that the member is negative for the presence of the following active infections: HIV, hepatitis B virus, and hepatitis C virus;
10. Member does not have advanced liver disease (*see Appendix E*);
11. Member does not have current malignancy or immunodeficiency disorder;
12. Documentation of member's body weight in kg;
13. Dose contains a minimum of 3 x 10^6 CD34+ cells/kg.

Approval duration: 6 months (one-time infusion per lifetime)

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I

1. Continued therapy will not be authorized as Casgevy is indicated to be dosed one time only.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACS: acute chest syndrome
ANC: absolute neutrophil count
CBC: complete blood count
FDA: Food and Drug Administration
HbF: fetal hemoglobin
HIV: human immunodeficiency virus
HSCT: hematopoietic stem cell transplantation
MCV: mean corpuscular volume
NHLBI: National Heart, Lung, and Blood Institute
pRBC: packed red blood cells
SCD: sickle cell disease
TDT: transfusion dependent β-thalassemia
ULN: upper limit of normal
VOC: vaso-occlusive crisis
WBC: white blood cells

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
SCD		
hydroxyurea‡	*Age ≥ 18 years* Initial: 15 mg/kg/dose PO QD, rounded to the nearest 500-mg increment* *Age 9 months to 17 years* Initial: 20 mg/kg/dose PO QD* ** Increase by 5 mg/kg/day every 8 weeks until mild myelosuppression (ANC 2,000 to 4,000/microliter) achieved.*	35 mg/kg/day
Droxia® (hydroxyurea)	*Age ≥ 18 years* Initial: 15 mg/kg/day PO single dose; based on blood counts, may increase by 5 mg/kg/day every 12 weeks to a max 35 mg/kg/day	35 mg/kg/day
Siklos® (hydroxyurea)	*Age ≥ 18 years* Initial: 15 mg/kg PO QD*	35 mg/kg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
SCD		
	<u>*Age 2 years to 17 years*</u> Initial: 20 mg/kg PO QD* **Based on blood counts, may increase by 5 mg/kg/day every 8 weeks or if a painful crisis occurs*	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
ǂ Off-label, 2014 NHLBI SCD guideline-supported dosing regimen

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- Hydroxyurea dose titration for SCD: Members should obtain complete blood counts (CBC) with white blood cell (WBC) differential and reticulocyte counts at least every 4 weeks for titration. The following lab values indicate that it is safe to increase dose.
  - Absolute neutrophil count (ANC) in adults ≥ 2,000/µL, or ANC ≥ 1,250/µL in younger patients with lower baseline counts
  - Platelet count ≥ 80,000/µL

  If neutropenia or thrombocytopenia occurs: hydroxyurea dosing is held, CBC and WBC differential are monitored weekly, and members can restart hydroxyurea when values have recovered.
- Conversion of RBC units from mL: 1 RBC unit in these criteria refers to a quantity of pRBC approximately 200-350 mL.
  - For sites who use transfusion bags within this range, or ≥ 350 mL, the conversion in units should be done by dividing the volume transfused to the patient by 350 mL.
  - For sites who use transfusion bags < 200 mL, the conversion in units should be done by dividing the volume transfused to the patient by 200 mL.

Appendix E: Advanced Liver Disease
- Examples of advanced liver disease include, but are not limited to, the following:
  - Cirrhosis
  - Bridging or significant fibrosis
  - Active hepatitis
  - Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value > 3x the upper limit of normal (ULN)
  - Baseline prothrombin time or partial thromboplastin time > 1.5x ULN

Appendix F: Genetic Confirmation of β-Thalassemia

β-Thalassemia Genotype Examples
β^0/β^0
β^+/β^+
β^0/β^+
β^0/β^+ (IVS-I-110)

β-Thalassemia Genotype Examples
β^E/β^+
β^E/β^0

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
SCD, TDT	Minimum recommended dose: 3 x 10^6 $CD34^+$ cells/kg of body weight IV	Not applicable

VI. Product Availability

Single-dose cell suspension: up to nine vials, with each vial containing 4 to 13 × 10^6 CD34+ cells/mL suspended in 1.5 to 20 mL cryopreservative medium

VII. References

1. Casgevy Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc.; January 2024. Available at www.casgevy.com. Accessed November 18, 2024.
2. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-CaS9 gene editing for sickle cell disease and β-thalassemia. N Engl J Med 2021; 384:252-60. www.doi.org/10.1056/NEJMoa2031054.
3. ClinicalTrials.gov. A safety and efficacy study evaluating CTX001 in subjects with severe sickle cell disease. Last updated June 1, 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT03745287. Accessed November 18, 2024.
4. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Evidence-based management of sickle cell disease: Expert Panel Report, 2014. National Heart, Lung, and Blood Institute (NHLBI). Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed November 18, 2024.
5. Clinical Pharmacology [database online]. Philadelphia, PA: Elsevier. Updated periodically. Available at: http://www.clinicalkey.com/pharmacology. Accessed November 18, 2024.
6. ClinicalTrials.gov. A safety and efficacy study evaluating CTX001 in subjects with transfusion-dependent β-thalassemia. Last updated June 1, 2022. Available at: https://clinicaltrials.gov/study/NCT03655678. Accessed January 21, 2024.
7. Cappellini MD, Farmakis D, Porter J, et al. Guidelines for the management of transfusion dependent thalassemia (TDT) 4th Edition (Version 2.0). Thalassemia International Federation (2021). Available at: https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-transfusion-dependent-thalassaemia-4th-edition-2021-v2/. Accessed November 18, 2024.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3392	Injection, exagamglogene autotemcel, per treatment

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	11.08.22	02.23
1Q 2024 annual review: drug is now FDA-approved – criteria updated per FDA labeling: clarified that genetic confirmation of genotype is required; added definitions of severe VOC; added hydroxyurea failure criterion per standard of care for SCD; added criteria that member is negative for the presence of active HIV, hepatitis B virus, hepatitis C virus, advanced liver disease, current malignancy, and current immunodeficiency disorder; clarified minimum Casgevy dose required; approval duration revised to 6 months to allow for gene therapy preparation; references reviewed and updated; references reviewed and updated.	01.16.24	02.24
RT2: criteria updated with newly approved indication for TDT per FDA labeling and pivotal trial: added additional option for meeting transfusion dependence with receipt of ≥ 8 transfusions of pRBC per year for the previous two years to align with Zynteglo; added associated α-thalassemia and > 1 alpha chain deletion, alpha multiplications, and associated sickle cell β-thalassemia as exclusions per specialist feedback; added criteria that member is negative for active HIV, hepatitis B virus, hepatitis C virus, advanced liver disease, current malignancy, and current immunodeficiency disorder; clarified minimum Casgevy dose required; revised initial approval duration to 6 months to allow adequate time for gene therapy manufacture; references reviewed and updated.	03.12.24	05.24
HCPCS code added [J3392] and removed codes [J3590,C9399].	11.06.24	
1Q 2025 annual review: for both SCD and TDT indications, added criterion for documentation of member's body weight for verification of weight-based dose; references reviewed and updated.	11.18.24	02.25
Updated language under Policy/Criteria to effectively redirect prior authorization reviews to Precision Drug Action Committee (PDAC) Utilization Management Review.	11.04.25	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It 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 physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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