Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the Blue Cross Blue Shield Association

Title: Lyfgenia

Professional / Institutional
Original Effective Date: August 1, 2024
Latest Review Date: December 26, 2025
Current Effective Date: December 26, 2025

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

Indication	Dose
Sickle-Cell Disease	Lyfgenia is provided as a single dose for infusion containing a suspension of CD34+ cells in one to four infusion bags. • The minimum recommended dose of Lyfgenia is 3×10^6 CD34+ cells/kg.
- *Mobilization should occur using a CXCR4 (e.g., plerixafor) in the absence of G-CSF* - *Myeloablative conditioning (e.g., busulfan) should not occur until Lyfgenia (and back-up cell collection) are received. Prophylaxis for hepatic veno-occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome should be considered.* - *Lyfgenia must be administered at least 48 hours after the last dose of the myeloablative conditioning.* - *Lyfgenia is for autologous use only. Before infusion, confirm that the patient's identity matches the unique patient identifiers on the Lyfgenia bag(s). Do not infuse if the information on the patient-specific label does not match the intended patient.*	

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

I. Length of Authorization

- Initial: Prior authorization validity will be provided initially for one treatment course (1 dose of Lyfgenia).
- Renewal: Prior authorization validity may not be renewed.

II. Dosing Limits

Max Units (per dose and over time) [HCPS Unit]:

- 1 billable unit for one dose

III. Initial Approval Criteria [1]

Submission of supporting clinical documentation (including but not limited to medical records, chart notes, lab results, and confirmatory diagnostics) related to the medical necessity criteria is REQUIRED on all requests for authorizations. Records will be reviewed at the time of submission as part of the evaluation of this request. Please provide documentation related to diagnosis, step therapy, and clinical markers (i.e., genetic, and mutational testing) supporting initiation when applicable. Please provide documentation via direct upload through the PA web portal or by fax. Failure to submit the medical records may result in the denial of the request due to inability to establish medical necessity in accordance with policy guidelines.

Coverage is provided in the following conditions:

- Patient is at least 12 years of age; **AND**
- Provider has considered use of prophylaxis therapy for seizures with agents other than phenytoin prior to initiating myeloablative conditioning; **AND**
- Patient will be monitored for hematologic malignancies periodically after treatment; **AND**
- Must not be administered concurrently with live vaccines while immunosuppressed; **AND**
- Patient does not have a history of hypersensitivity to dimethyl sulfoxide (DMSO) or dextran 40; **AND**
- Patient is HIV negative as confirmed by a negative HIV test prior to mobilization (*Note: Patients who have received Lyfgenia are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a possible false-positive PCR assay test result for HIV. Therefore, patients who have received Lyfgenia should not be screened for HIV infection using a PCR-based assay.)*; **AND**
- Patient will not receive therapy concomitantly with any of the following:
    - Hydroxyurea for at least 2 months prior to mobilization and until all cycles of apheresis are completed *(Note: If hydroxyurea is administered between*

mobilization and conditioning, discontinue 2 days prior to initiation of conditioning); **AND**

- Iron chelators for at least 7-days prior to mobilization or conditioning and for 6 months post-treatment for myelosuppressive iron chelators (e.g., deferiprone) OR 3-months post-treatment for non-myelosuppressive iron chelators; **AND**
- Disease-modifying agents (e.g., L-glutamine, crizanlizumab) for at least 2 months prior to mobilization; **AND**
- Prophylactic HIV anti-retroviral therapy *(Note: Patients receiving prophylactic ART should stop therapy for at least one month prior to mobilization and until all cycles of apheresis are completed)*; **AND**
- Mobilization of stem cells using granulocyte-colony stimulating factor (G-CSF); **AND**
- Erythropoietin for at least 2 months prior to mobilization; **AND**

- Patient has not received other gene therapy [e.g., Casgevy™ (exagamglogene autotemcel)] **§**; **AND**
- Patient is a candidate for autologous hematopoietic stem cell transplant (HSCT) and has not had a prior allogeneic transplant; **AND**
- For patients under 18 years of age, the patient does not have a known and available suitable 10/10 human leukocyte antigen matched related donor willing to participate in an allogeneic HSCT; **AND**
- Patient will be transfused at least twice (once each month) prior to mobilization to reach a target Hb of 8-10 g/dL (less than 12 g/dL) and <30% HbS; **AND**

§ *Requests for subsequent use of lovotibeglogene after receipt of exagamglogene autotemcel will be evaluated on a case-by-case basis*

Sickle Cell Disease [1-3] † Φ

- Patient has a confirmed diagnosis of sickle-cell disease with one of the following genotypes βS/βS or βS/β0 or βS/β+ (Note: Additional genotypes will be considered on a case-by-case basis based on disease severity) as determined by one of the following:
  - Identification of significant quantities of HbS with or without an additional abnormal β-globin chain variant by hemoglobin assay; **OR**
  - Identification of biallelic *HBB* pathogenic variants where at least one allele is the p.Glu6Val pathogenic variant on molecular genetic testing; **AND**
- Patient does NOT have disease with more than two α-globin gene deletions; **AND**
- Patient has uncontrolled disease despite treatment with hydroxyurea OR crizanlizumab at any point in the past *(Note: trial of crizanilzumab not applicable to patients less than 16 years of age)* OR has experienced intolerance OR has required repeat transfusions to treat symptomatic disease and/or reduce the risk of stroke; **AND**

- Patient has severe, symptomatic disease despite treatment with supportive care measures, as experienced by one or more of the following:
    - Patient has echocardiographic evidence of a tricuspid regurgitant jet velocity (TRJV) of > 2.5 m/s; **OR**
    - Patient has had or has a history of an overt stroke (Note: Defined as a sudden neurologic change lasting more than 24 hours that is accompanied by cerebral MRI changes); **OR**
    - Patient has experienced an 'acute chest syndrome' episode, defined as an acute event with pneumonia-like symptoms and the presence of a new pulmonary infiltrate in the previous 2 years; **OR**
    - Patient experienced two or more vaso-occlusive events/crises (VOE/VOC) ***** in the previous year

**VOE/VOC is defined as an event requiring a visit to a medical facility for evaluation which results in a diagnosis of such being documented due to one (or more) of the following: acute pain, acute chest syndrome, acute splenic sequestration, acute hepatic sequestration, priapism lasting > 2 hours AND necessitating subsequent interventions such as opioid pain management, non-steroidal anti-inflammatory drugs, RBC transfusion, etc.*

† FDA Approved Indication(s); **‡** Compendia Recommended Indication(s); **Φ** Orphan Drug

IV. Renewal Criteria [1,3]

- Duration of authorization has not been exceeded *(refer to Section I*).

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.

CLINICAL RATIONALE

See package insert for FDA preshttps://dailymed.nlm.nih.gov/dailymed/index.cfm

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

HCPCS:

- J3394 – Injection, lovotibeglogene autotemcel, per treatment; 1 billable unit = 1 treatment

NDC:

- Lyfgenia is supplied in one to four infusion bags containing a frozen suspension of genetically modified autologous cells, enriched for CD34+ cells, 20 mL infusion bag, overwrap, and metal cassette: 73554-1111-xx

REVISIONS	
Posted 07-01-2024 Effective 08-01-2024	New medical policy added to the bcbsks.com web site. Policy maintained by Prime Therapeutics LLC.
Posted 10-22-2024 Effective 11-21-2024	Clinical Criteria Updated. Section I: Length of Authorization • Changed "may not" to "will not" Section III: Initial Approval Criteria • Added criteria requirement that patient has not had a prior HSCT • Added criteria that for patients under the age of 18, the patient must not have a known and suitable 10/10 human leukocyte antigen matched related donor willing to participate in an allogenic HSCT • Added criteria requirement that patient will be transfused prior to apheresis and at least 8 weeks prior to initiation of myeloablative conditioning to meet Hb and HbS goals • Added criteria requirement for sickle cell disease that patient must have symptomatic sickle cell disease despite treatment with hydroxyurea or add on therapy or has an intolerance to hydroxyurea • Removed criteria requirement that patients with 4 events/crises within the past
2-25-2025	Updated Coding Section ▪ Removed J3590 ▪ Added J3394
2-25-2025	*Edited requirement for seizure prophylaxis during myeloablative conditioning to not include phenytoin (Phenytoin was not used for anti-seizure prophylaxis in clinical trials because of its induction of cytochrome P-450 and resultant increased clearance of busulfan, the agent used for myeloablative conditioning) (p. 1)

REVISIONS	
04-08-2025	Updated Section III Initial Approval Criteria ▪ Edited requirement for seizure prophylaxis during myeloablative conditioning to not include phenytoin (Phenytoin was not used for anti-seizure prophylaxis in clinical trials because of its induction of cytochrome P-450 and resultant increased clearance of busulfan, the agent used for myeloablative conditioning)
	Policy maintained by Prime Therapeutics LLC.
Posted: 11-26-2025 Effective: 12-26-2025	Initial Approval Criteria ▪ Added: to the submission box "Failure to submit the medical records may result in the denial of the request due to inability to establish medical necessity in accordance with policy guidelines." Coverage is provided in the following conditions: Patient will not receive therapy concomitantly with any of the following: ▪ Removed: "Myelosuppressive iron chelators (e.g., deferiprone, etc.) for 7-days prior to mobilization, conditioning, and 6 months post-treatment; AND" ▪ Added: "Iron chelators for at least 7-days prior to mobilization or conditioning and for 6 months post-treatment for myelosuppressive iron chelators (e.g., deferiprone) OR 3-months post-treatment for non-myelosuppressive iron chelators; AND Sickle Cell Disease 1-3 † Φ ▪ Removed: "Patient has symptomatic disease despite treatment with hydroxyurea at any point in the past OR add-on therapy (e.g., crizanlizumab, voxelotor, etc.) OR has experienced intolerance; AND" ▪ Added: "Patient has uncontrolled disease despite treatment with hydroxyurea OR crizanlizumab at any point in the past *(Note: trial of crizanilzumab not applicable to patients less than 16 years of age)* OR has experienced intolerance OR has required repeat transfusions to treat symptomatic disease and/or reduce the risk of stroke; AND" ▪ Added: "Patient has severe, symptomatic disease despite treatment with supportive care measures, as experienced by one or more of the following: o Patient has echocardiographic evidence of a tricuspid regurgitant jet velocity (TRJV) of > 2.5 m/s; OR o Patient has had or has a history of an overt stroke (Note: Defined as a sudden neurologic change lasting more than 24 hours that is accompanied by cerebral MRI changes); OR o Patient has experienced an 'acute chest syndrome' episode, defined as an acute event with pneumonia-like symptoms and the presence of a new pulmonary infiltrate in the previous 2 years; OR"
	Medical Policy maintained by Prime Therapeutics LLC

REFERENCES

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