LYFGENIA™ (lovotibeglogene autotemcel)
Sample Letter of Appeal for Denial of Coverage

To the Treating Physician:

This sample letter, provided by bluebird bio, Inc., is for informational purposes only, providing an example of language that may be required or helpful when filing an appeal to overturn a denial of coverage for LYFGENIA™ (lovotibeglogene autotemcel) suspension for intravenous infusion. Use of this information does not constitute medical or legal advice and does not guarantee reimbursement for coverage. It is not intended to be a substitute for, or an influence on, the independent clinical decision of the prescribing healthcare professional.

It also includes examples of types of documentation to include to support their clinical decision-making. Attachments to include with the letter of appeal are the original prior authorization (PA) form and letter of medical necessity submitted, a copy of the denial or explanation of benefits (EOB), and any other additional supporting documents.

When sending a letter of appeal for denial of coverage to a third-party payer for review, ensure that you submit under your practice / individual physician letterhead.

The following pages are a sample that may be customized to use as a statement of appeal for your patients. Use of this sample letter is not required.

Indication

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.

Important Safety Information

Boxed WARNING: HEMATOLOGIC MALIGNANCY

Hematologic malignancy has occurred in patients treated with LYFGENIA. Monitor patients closely for evidence of malignancy through complete blood counts at least every 6 months and through integration site analysis at Months 6, 12, and as warranted.

Important Safety Information (cont'd)

Hematologic Malignancy

Hematologic malignancy has occurred in patients treated with LYFGENIA (Study 1, Group A). At the time of initial product approval, two patients treated with an earlier version of LYFGENIA using a different manufacturing process and transplant procedure (Study 1, Group A) developed acute myeloid leukemia (AML). One patient with α-thalassemia trait (Study 1, Group C) has been diagnosed with myelodysplastic syndrome (MDS).

The additional hematopoietic stress associated with mobilization, conditioning, and infusion of LYFGENIA, including the need to regenerate the hematopoietic system, may increase the risk of a hematologic malignancy. Patients with sickle cell disease have an increased risk of hematologic malignancy as compared to the general population.

Patients treated with LYFGENIA (lovotibeglogene autotemcel) may develop hematologic malignancies and should have lifelong monitoring. Monitor for hematologic malignancies with a complete blood count (with differential) at least every 6 months for at least 15 years after treatment with LYFGENIA, and integration site analysis at Months 6, 12, and as warranted.

In the event that a malignancy occurs, contact bluebird bio at 1-833-999-6378 for reporting and to obtain instructions on collection of samples for testing.

Post-Marketing Long Term Follow-Up Study: Patients who intend to receive treatment with LYFGENIA are encouraged to enroll in the study, as available, to assess the long-term safety of LYFGENIA and the risk of malignancies occurring after treatment with LYFGENIA by calling bluebird bio at 1-833-999-6378. The study includes monitoring (at pre-specified intervals) for clonal expansion.

Delayed Platelet Engraftment

Delayed platelet engraftment has been observed with LYFGENIA. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia. Two patients (4%) required more than 100 days post treatment with LYFGENIA to achieve platelet engraftment.

Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise.

Neutrophil Engraftment Failure

There is a potential risk of neutrophil engraftment failure after treatment with LYFGENIA. Neutrophil engraftment failure is defined as failure to achieve three consecutive absolute neutrophil counts (ANC) $\geq 0.5 \times 10^9$ cells/L obtained on different days by Day 43 after infusion of LYFGENIA. Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs in a patient treated with LYFGENIA, provide rescue treatment with the back-up collection of CD34+ cells.

Important Safety Information (cont'd)

Insertional Oncogenesis

There is a potential risk of lentiviral vector-mediated insertional oncogenesis after treatment with LYFGENIA.

Hypersensitivity Reactions

Allergic reactions may occur with the infusion of LYFGENIA. The dimethyl sulfoxide (DMSO) or dextran 40 in LYFGENIA may cause hypersensitivity reactions, including anaphylaxis.

Anti-retroviral Use

Patients should not take prophylactic HIV anti-retroviral medications for at least one month prior to mobilization and until all cycles of apheresis are completed. There are some long-acting anti-retroviral medications that may require a longer duration of discontinuation for elimination of the medication. If a patient is taking anti-retrovirals for HIV prophylaxis, confirm a negative test for HIV before beginning mobilization and apheresis of CD34+ cells.

Hydroxyurea Use

Patients should not take hydroxyurea for at least 2 months prior to mobilization and until all cycles of apheresis are completed. If hydroxyurea is administered between mobilization and conditioning, discontinue 2 days prior to initiation of conditioning.

Iron Chelation

Drug-drug interactions between iron chelators and the mobilization process and myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to initiation of mobilization or conditioning. Do not administer myelosuppressive iron chelators (e.g., deferiprone) for 6 months post-treatment with LYFGENIA (lovotibeglogene autotemcel). Non-myelosuppressive iron chelation should be restarted no sooner than 3 months after LYFGENIA infusion. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Interference with PCR-based Testing

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.

Adverse Reactions

The most common adverse reactions ≥ Grade 3 (incidence ≥ 20%) were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia.

Three patients died during LYFGENIA clinical trials; one from sudden cardiac death due to underlying disease and two from acute myeloid leukemia who were treated with an earlier version of LYFGENIA using a different manufacturing process and transplant procedure (Study 1, Group A).

Important Safety Information (cont'd)

Pregnancy/Lactation

Advise patients of the risks associated with myeloablative conditioning agents, including on pregnancy and fertility.

LYFGENIA should not be administered to women who are pregnant, and pregnancy after LYFGENIA infusion should be discussed with the treating physician.

LYFGENIA is not recommended for women who are breastfeeding, and breastfeeding after LYFGENIA infusion should be discussed with the treating physician.

Females and Males of Reproductive Potential

A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before LYFGENIA administration.

Women of childbearing potential and men capable of fathering a child should use an effective method of contraception (intra-uterine device or combination of hormonal and barrier contraception) from start of mobilization through at least 6 months after administration of LYFGENIA.

Advise patients of the options for fertility preservation.

[Today's Date]
[Name of Insurance Company] [Address of Insurance Company] [City], [State], [Zip Code]

Re: [Patient Name], [DOB], [Parent/Legal Guardian's Name (If Applicable)]
Policy Number: [Enter Number]
Group Number: [Enter Number]
Medicaid Number: [Enter Number (If Applicable)]
ICD-10-CM Diagnosis Code(s): [Enter Code(s)]
Denial Reference Number: [Enter Number]

LETTER OF APPEAL FOR DENIAL OF COVERAGE FOR LYFGENIA™

Dear [Medical Director's Name],

I am writing on behalf of my patient, [Enter Name], to appeal a denial of coverage for LYFGENIA (lovotibeglogene autotemcel), a gene therapy for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events. My patient [is X years old] and was diagnosed with sickle cell disease on [Enter Diagnosis Date]. I recently performed a consultation regarding the patient's clinical eligibility for LYFGENIA on [Enter Date].

According to your letter, coverage was denied due to [reason stated in the denial letter]. In summary, treatment with LYFGENIA is medically necessary and appropriate for [patient name] and should be a covered treatment. This letter outlines relevant details of [patient name]'s medical history and prognosis, as well as the treatment rationale that supports my decision to prescribe LYFGENIA.

DISEASE OVERVIEW
Sickle cell disease (SCD) is a serious, progressive, and debilitating[1] genetic disease caused by a point mutation in the β-globin gene that induces hemoglobin (Hb) to polymerize and red blood cells (RBCs) to sickle, leading to the hallmark characteristics of frequent[2], painful vaso-occlusive events (VOEs), and anemia.[1]

LYFGENIA addresses the underlying genetic cause of SCD without the need of a donor.

CLINICAL TRIALS OVERVIEW[3]

The efficacy of LYFGENIA (lovotibeglogene autotemcel) was studied in a single-arm, 24-month, open-label, multicenter Phase 1/2 study (Study 1-C) and continued on a long-term follow-up study. The VOE-evaluable population included 32 patients with a history of at least 4 VOEs in the 24 months prior to informed consent.

VOEs were defined as any of the following events requiring evaluation at a medical facility:

- an episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more than 2 hours

- acute chest syndrome (ACS)
- acute hepatic sequestration
- acute splenic sequestration

Severe VOE (sVOE) were defined as either of the following events:

- VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit
- priapism requiring any level of medical attention

The efficacy outcomes of LYFGENIA were complete resolution of VOEs (VOE-CR) and severe VOEs (sVOE-CR) between 6 months and 18 months after infusion of LYFGENIA in Study 1-C. Of 32 VOE-evaluable patients in Study 1-C, 28 (88%, 95% CI: 71, 97) achieved VOE-CR and 30 patients achieved sVOE-CR (94%, 95% CI: 79, 99).

Safety was based on 45 patients with sickle cell disease in one open-label, single-arm clinical trial and one long-term follow-up study. In the study 33 (73%, 33/45) patients who received LYFGENIA experienced at least one serious adverse event (SAE). Most SAEs were related to conditioning or underlying disease.

Most common adverse reactions ≥ Grade 3 (incidence ≥ 20%) were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia. Three patients died during LYFGENIA clinical trials; one from sudden cardiac death due to underlying disease and two from acute myeloid leukemia who were treated with an earlier version of LYFGENIA using a different manufacturing process and transplant procedure (Study 1, Group A).

LYFGENIA MECHANISM OF ACTION[3]

LYFGENIA (lovotibeglogene autotemcel) adds functional copies of a modified βA-globin gene (threonine [T] replaced with glutamine [Q] at position 87, T87Q or βA-T87Q-globin) into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with BB305 LVV. After LYFGENIA infusion, the transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells containing biologically active βA^{-T87Q}-globin that will combine with α-globin to produce functional Hb containing βA^{-T87Q}-globin (HbA^{T87Q}). HbA^{T87Q} has similar oxygen-binding affinity and oxygen hemoglobin dissociation curve to wild type HbA, reduces intracellular and total hemoglobin S (HbS) levels, and is designed to sterically inhibit polymerization of HbS thereby limiting the sickling of red blood cells.

References:

1. Kanter J, et al. Lovo-cel gene therapy for sickle cell disease: treatment process evolution and outcomes in the initial groups of the HGB-206 study. Am J Hematol. 2023 Jan;98(1):11-22
2. Kato GJ, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010.
3. LYFGENIA [prescribing information], Somerville, MA; bluebird bio, Inc.; December 2023.

SUMMARY OF PATIENT'S MEDICAL HISTORY

[Treating physician to provide patient level detailed clinical assessment that explains rationale for the use of LYFGENIA. This may include summary of the patient's likely prognosis or disease progression without treatment with LYFGENIA]

These may include details addressing the specific denial reason(s), such as:

- **Patient's diagnosis and current condition/ICD-10 code(s)**
- **Current age (12 or older)**
- **Documentation of the history of vaso-occlusive events (e.g., frequency of VOEs, VOE type, VOE complications)**
- **Additional disease-related symptoms that may be relevant**
- **Relevant medical history documentation, which may also include:**
  - **Lack of a clinically suitable, willing, fully matched sibling donor**
  - **Information pertaining to genetic testing**
  - **Documentation, if available, of prior treatments and responses to those treatments, including history of hydroxyurea failure or intolerance at any point in the past**
  - **Patient comorbidities that could serve as contraindications to certain other treatments, if applicable**
  - **Performance status measures (Karnofsky for over 16 years of age & Lansky for under 16 years of age)**

RECOMMENDED MEDICAL INTERVENTION

[Note: Exercise your medical judgment and discretion when providing a diagnosis and characterization of the patient's medical conditions and your recommendations. Provide your clinical rationale for treatment while considering the health plan's medical policy criteria for LYFGENIA.]

As a [Enter Specialty (e.g., "board-certified hematologist")] and the treating physician, I am recommending LYFGENIA (lovotibeglogene autotemcel) for my patient, based on their diagnosis and medical history, my clinical experience, and LYFGENIA'S FDA-approved use. In my professional opinion, LYFGENIA is medically necessary for this patient. I have reviewed the potential benefits and counseled them on the risks associated with LYFGENIA treatment, including the steps for administration with the patient AND [patient's parents OR patient's legal guardians].

[Treating Physician to Insert Clinical Rationale for Prescribing LYFGENIA Including Any Supportive Chart Notes]

Please contact me if any additional information is required to ensure the prompt approval of the treatment(s) in question.

Sincerely,

[Enter Physician's Name and Signature]
[Enter Name(s) of Additional Care Team Member(s) and Signature(s) (e.g., physicians, other specialties)]