ZYNTEGLO™ (betibeglogene autotemcel) Sample Letter of Medical Necessity

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 responding to a request from a patient's health plan. 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. Please note that some payers may have specific forms that must be completed in order to request prior authorization or to document medical necessity. When sending this information 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 medical necessity/appeal for your patients. Use of this sample letter is not required.

Indication

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

Important Safety Information

Delayed Platelet Engraftment

Delayed platelet engraftment has been observed with ZYNTEGLO treatment. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia; 15% of patients had ≥ Grade 3 decreased platelets on or after Day 100.

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.

Risk of Neutrophil Engraftment Failure

There is a potential risk of neutrophil engraftment failure after treatment with ZYNTEGLO. Neutrophil engraftment failure is defined as failure to achieve three consecutive absolute neutrophil counts (ANC) ≥ 500 cells/microliter obtained on different days by Day 43 after infusion of ZYNTEGLO. Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs in a patient treated with ZYNTEGLO, provide rescue treatment with the back-up collection of CD34+ cells.

Risk of Insertional Oncogenesis

There is a potential risk of lentiviral vector (LVV)-mediated insertional oncogenesis after treatment with ZYNTEGLO.

Please see Important Safety Information on pages 1-3 and full Prescribing Information for ZYNTEGLO.

Important Safety Information (cont'd)

Risk of Insertional Oncogenesis (cont'd)

Patients treated with ZYNTEGLO (betibeglogene autotemcel) may develop hematologic malignancies and should be monitored lifelong. Monitor for hematologic malignancies with a complete blood count (with differential) at Month 6 and Month 12 and then at least annually for at least 15 years after treatment with ZYNTEGLO, 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.

Hypersensitivity Reactions

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

Anti-retroviral and Hydroxyurea Use

Patients should not take prophylactic HIV anti-retroviral medications or hydroxyurea for at least one month prior to mobilization, or for the expected duration for elimination of the medications, and until all cycles of apheresis are completed. If a patient requires anti-retrovirals for HIV prophylaxis, then confirm a negative test for HIV before beginning mobilization and apheresis of CD34+ cells.

Interference with Serology Testing

Patients who have received ZYNTEGLO are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a false-positive test for HIV. Therefore, patients who have received ZYNTEGLO should not be screened for HIV infection using a PCR- based assay.

Adverse Reactions

The most common non-laboratory adverse reactions (≥20%) were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus. The most common Grade 3 or 4 laboratory abnormalities (>50%) include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.

Drug Interactions

Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. The prescribing information for the iron chelator(s) and the myeloablative conditioning agent should be consulted for the recommendations regarding co-administration with CYP3A substrates.

Some iron chelators are myelosuppressive. After ZYNTEGLO infusion, avoid use of these iron chelators for 6 months. If iron chelation is needed, consider administration of non-myelosuppressive iron chelators. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Important Safety Information (cont'd)

Pregnancy/Lactation

Advise patients of the risks associated with conditioning agents, including on pregnancy and fertility. ZYNTEGLO (betibeglogene autotemcel) should not be administered to women who are pregnant, and pregnancy after ZYNTEGLO infusion should be discussed with the treating physician.

ZYNTEGLO is not recommended for women who are breastfeeding, and breastfeeding after ZYNTEGLO 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 ZYNTEGLO 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 ZYNTEGLO.

Advise patients of the option to cryopreserve semen or ova before treatment if appropriate.

[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)]

REQUESTING EXPEDITED REVIEW FOR TREATMENT WITH ZYNTEGLO™

Dear [Medical Director's Name],

I am writing on behalf of my patient, [Enter Name], to document the medical necessity of ZYNTEGLO (betibeglogene autotemcel), a gene therapy for the treatment of patients with β-thalassemia who require regular red blood cell (RBC) transfusions. My patient was diagnosed on [Enter Diagnosis Date] and has been receiving regular RBC transfusions to manage their condition for [Enter Number of Months/Years]. I recently performed a consultation regarding the patient's clinical eligibility for ZYNTEGLO on [Enter Date]. Given their reliance on regular RBC transfusions, I am requesting expedited review and approval of ZYTENGLO for my patient.

DISEASE OVERVIEW[1]
Patients with beta-thalassemia (beta-thal) do not make enough healthy RBCs and typically need RBC transfusions every two to five weeks to reduce the symptoms of anemia. Patients with β-thalassemia who require regular RBC transfusions, also require chelation therapy, which is needed to reduce excess iron caused by chronic blood transfusions – all of which compounds the challenges of managing this disease. Addressing the underlying genetic cause of beta-thal through gene therapy has the potential to help patients achieve normal hemoglobin levels and eliminate the dependence on regular RBC transfusions.

While transfusions temporarily relieve symptoms associated with severe anemia, including fatigue, weakness, and shortness of breath, they do not address the underlying genetic cause of beta-thal and can lead to unavoidable iron overload. Iron overload resulting from beta-thalassemia or ongoing RBC transfusions requires chronic treatment with chelation therapy; even with chelation therapy, some patients remain significantly iron overloaded, and not all patients are adherent, due in part to tolerability issues. Despite advances in treatment and improved transfusion techniques, people with beta-thalassemia who require regular transfusions have been shown to have an increased risk for morbidity and mortality.

ZYNTEGLO CLINICAL TRIALS OVERVIEW[2]

FDA approval for ZYNTEGLO was based on the March 2021 data cut from bluebird bio's Phase 3 studies HGB-207 (Northstar-2; study 1) and HGB-212 (Northstar-3; study 2). bluebird bio is also conducting a long-term follow-up study, LTF-303 (study 3), to monitor safety and efficacy for people who have participated in bluebird bio-sponsored clinical studies through 15 years post-treatment.

The efficacy and safety of ZYNTEGLO (betibeglogene autotemcel) was evaluated in 2 ongoing Phase 3 open-label, single-arm, 24-month, multicenter studies (study 1 enrolled non-β^0/β^0 genotype and study 2 enrolled β^0/β^0 or non-β^0/β^0 (IVS-I-110/IVS-I-110 or IVS-I-110/ β^0) genotypes) in 41 patients aged 4 to 34 years with β-thalassemia requiring regular RBC transfusions. Patients were considered to be eligible for the Phase 3 studies if they had a history of transfusions of at least 100 mL/kg/year of packed red blood cells (pRBCs) or with 8 or more transfusions of pRBCs per year in the 2 years preceding enrollment. In Phase 3 studies, 89% (32/36) of evaluable patients across ages and genotypes achieved transfusion independence, which is defined as a weighted average hemoglobin ≥9 g/dL without any pRBC transfusions for a continuous period of ≥12 months at any time during the study. The median weighted average total hemoglobin level was 11.5 g/dL (min, max: 9.3-13.7) in patients who achieved transfusion independence. In the phase 3 studies, 20/32 patients who achieved TI were not receiving chelation as of last follow-up. Iron removal therapy after ZYNTEGLO was managed at physician discretion.

The most common non-laboratory adverse reactions (≥ 20%) were mucositis, febrile neutropenia, vomiting, pyrexia (fever), alopecia (hair loss), epistaxis (nose bleed), abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus (itch).

The most common Grade 3 or 4 laboratory abnormalities (> 50%) include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.

ZYNTEGLO MECHANISM OF ACTION[2]

ZYNTEGLO adds functional copies of a modified β-globin gene into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with BB305 LVV. After ZYNTEGLO infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce RBCs containing biologically active $\beta^{A\text{-}T87Q}$-globin (a modified β-globin protein) that will combine with α-globin to produce functional adult Hb containing βA-T87Q-globin (HbAT87Q). βA-T87Q-globin can be quantified relative to other globin species in peripheral blood using high-performance liquid chromatography. βA-T87Q-globin expression is designed to correct the β/α-globin imbalance in erythroid cells of patients with β-thalassemia and has the potential to increase functional adult HbA and total Hb to normal levels and eliminate dependence on regular pRBC transfusions.

References:

1. Cappellini MD, et al., Guidelines for Management of Transfusion-dependent Thalassaemia (TDT). Nicosia, Cyprus: Thalassaemia International Federation; 2021.

2. ZYNTEGLO [prescribing information], Somerville, MA; bluebird bio, Inc.; August 2022.

SUMMARY OF PATIENT'S MEDICAL HISTORY

[Treating physician to provide patient level details that would identify the specific clinical criteria for the use of ZYNTEGLO.]

These may include details such as:

- **Patient's diagnosis and current condition/ICD-10 code(s)**
- **Age at time of diagnosis**

Please see Important Safety Information on pages 1-3 and full Prescribing Information for ZYNTEGLO.

- **Current age**
- **Number of transfusions required per month, per year**
- **Disease related symptoms that would support the medical need**
- **Relevant medical history**
- **Information pertaining to and genetic testing**
- **Previous treatments/therapies**
- **and patient's response to these treatments/therapies (if applicable)**

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 ZYNTEGLO.]

As the treating physician, I am recommending ZYNTEGLO (betibeglogene autotemcel) for my patient, based on their diagnosis and medical history, my clinical experience, and ZYNTEGLO's FDA-approved use. In my professional opinion, ZYNTEGLO is medically necessary for this patient. I have reviewed the potential benefits and counseled them on the risks associated with ZYNTEGLO 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 ZYNTEGLO 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]