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Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 10/12/2023

Zynteglo® (betibeglogene autotemcel)

HCPCS: J3590

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

- A. Coverage of the requested drug is provided when all the following are met:
 - a. FDA approved indication
 - b. FDA approved age
 - c. Prescribed by or in consultation with a hematologist or transplant physician
 - d. Genetic testing confirming diagnosis of β -thalassemia
 - e. Must not have hemoglobin S/ β -thalassemia or α -thalassemia
 - f. Must be considered transfusion-dependent with a history of at least 100 mL/kg/year of packed red blood cells (pRBC) in the previous two years OR be managed under standard thalassemia guidelines with ≥ 8 transfusions of pRBCs per year in the previous two years
 - g. Must not have
 - i. A prior hematopoietic stem cell transplant (HSCT) or currently be eligible for a HSCT with a willing and able HLA matched donor as determined by a hematologist and/or stem cell transplant specialist
 - ii. Presence of HIV-1 or HIV-2 infection
 - iii. Any prior malignancy with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin
 - iv. Myeloproliferative or significant immunodeficiency disorder unless patients meet any of the following:
 - 1. Vaccinated against hepatitis B (hepatitis B surface antibody-positive) and negative for other markers of prior hepatitis B infection
 - 2. Had past exposure to HBV but were negative by assessment for HBV DNA
 - 3. Are positive for anti-hepatitis C antibodies and have negative HCV viral load
 - v. Uncorrected bleeding disorder
 - vi. Advanced liver disease unless liver biopsy shows no evidence of extensive bridging fibrosis, cirrhosis, or acute hepatitis defined as:
 - 1. Alanine transferases or direct bilirubin greater than 3 times the upper limit of normal (ULN)
OR
 - 2. Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the ULN suspected of arising from liver disease OR

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3. Magnetic resonance imaging (MRI) of the liver demonstrating clear evidence of cirrhosis
- h. Have not received prior treatment with any gene therapy or are being considered for treatment with any other gene therapy for beta-thalassemia
- i. The requesting physician attests to providing clinical outcome information within the Audaire Health™ provider portal as requested by BCBSM
- j. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria

- a. Quantity Limits: Align with FDA recommended dosing
- b. Authorization Period: 6 months
- c. Renewal Criteria: Not applicable as no further authorization will be provided

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Zynteglo is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with β -thalassemia who require regular red blood cell (RBC) transfusions.
- The term "thalassemia" refers to a group of blood disorders characterized by a decrease or absence of synthesis of normal hemoglobin globulin chains. According to the chain whose synthesis is impaired, the thalassemias are called α -, β -, γ -, δ -, $\delta\beta$ -, or $\epsilon\gamma\delta\beta$ -thalassemias. Beta-thalassemias result from a genetic defect in the HBB gene leading to a reduction in production of β -globulin chains, an excess of α -globulin chains, and a decrease in functioning hemoglobin. Low levels of hemoglobin cause a lack of oxygen in many parts of the body and anemia. People with anemia in beta-thalassemia often require lifelong blood transfusions for survival and subsequent treatment for iron overload due to these transfusions.
- The 2021 International Thalassemia Federation guidelines for transfusion-dependent thalassemias recommend diagnosis should begin with genetic testing because of the extreme diversity in clinical severity of thalassemia subtypes. The degree of excess nonfunctional α -chains is the major predictor of disease severity. The less β -globulin production, the more non-functional α -chains in the bloodstream. β_0 -thalassemia refers to the complete absence of production of β -globulin. When patients are homozygous for a β_0 -thalassemia gene, they cannot make any normal β -chains. β_+ -thalassemia indicates a mutation that presents decreased but not absent production of β -globulin. In thalassemia patients in which one or both of their β -thalassemia mutations are β_+ -mutations, the disorder may be less severe. Beta-thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires chronic transfusions early in life. Beta-thalassemia intermedia is a clinical diagnosis of a patient characterized by a less severe chronic anemia and a more variable clinical phenotype. Zynteglo was not studied in patients with S/ β -thalassemia or α -thalassemia. Patients with other β -thalassemia subtypes that were transfusion-dependent were included in the clinical trial.
- Treatment guidelines also recommend all patients undergo at least an annual comprehensive assessment at a thalassemia center. During such an assessment, recommendations are summarized after consultation with multiple specialists including a hematologist, a nurse specialist, a hepatologist, a cardiologist, an endocrinologist, a psychologist, a genetics counselor, a social worker, and a dietitian.

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- Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. Continuation of infusions can be assessed by withholding transfusions and monitoring weekly hemoglobin levels. If the hemoglobin drops under 7 g/dL on two occasions two weeks apart, then regular transfusions should be commenced. Guidelines define a patient as transfusion dependent when they are getting infusions of packed red blood cells every 2 – 5 weeks to maintain the pre-transfusion hemoglobin of 9 g/dL - 10.5 g/dL and the post-transfusion hemoglobin less than 14 - 15 g/dL. This translates to approximately 100 mL/kg/year of packed red blood cells.
- Safety and efficacy are being evaluated in 2 ongoing Phase III, open-label, single-arm, 24-month, multicenter trials, Northstar-2 and Northstar-3, in 41 patients aged 4 to 34 years with β -thalassemia requiring regular transfusions. Patients were eligible if they had a history of transfusions of at least 100 mL/kg/year of pRBCs or 8 or more transfusions of pRBCs per year in the 2 years preceding enrollment. Patients who had advanced liver disease defined as alanine transferases or direct bilirubin greater than 3 times the ULN, baseline prothrombin time or partial thromboplastin time greater than 1.5 times the ULN suspected of arising from liver disease, or MRI of the liver demonstrating clear evidence of cirrhosis were excluded. Patients also were not included in the trial if they had a prior HSCT or currently were eligible for a HSCT with an HLA matched family donor; presence of HIV-1 or HIV-2 infection; current immunodeficiency disorder or malignancy; or uncorrected bleeding disorder. The primary endpoint of both studies was transfusion independence. Of 22 patients evaluable in Northstar-2, 20 (95% CI: 71, 99) achieved transfusion independence with a median average hemoglobin during transfusion of 11.8 g/dL (9.7, 13.0). Northstar-3 had 14 patients who were evaluable and 12 (86%; 95% CI: 57, 98) achieved transfusion independence with a median average hemoglobin during transfusion independence of 10.20 g/dL (9.3, 13.7). All patients who achieved transfusion independence maintained it.
- There is currently no data supporting administration of Zynteglo following administration of another gene therapy. Zynteglo should not be given following any other gene therapy for β -thalassemia as safety and efficacy has not been established.
- The Audaire Health™ platform is a provider portal that is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the Audaire Health™ provider portal at the requested cadence.

References:

1. Zynteglo [prescribing information]. Somerville, MA: bluebird bio, Inc.; August 2022.
2. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non- β 0/ β 0 genotype β -thalassemia. NEJM. 2022; 386: 415 - 27.
3. Clinicaltrials.gov. A study evaluating the efficacy and safety of the LentiGlobin® BB305 drug product in participants with transfusion-dependent β -thalassemia (NCT03207009). Available at: <https://clinicaltrials.gov/ct2/show/NCT03207009>. Accessed on August 18, 2022.
4. National Organization for Rare Disorders. Beta-thalassemia. 2018. Available at: <https://rarediseases.org/rare-diseases/thalassemia-major/>. Accessed on August 18, 2022.
5. Cappellini MD, Cohen A, Porter J, et al. Guidelines for the management of transfusion dependent thalassemia. 2021. Available at: https://issuu.com/internationalthalassaemiafederatation/docs/final_guideline_4th. Accessed on August 18, 2022.

Policy History												
#	Date	Change Description										
1.3	Effective Date: 10/12/2023	Annual review – no changes to criteria at this time										
1.2	Effective Date: 11/01/2022	UM medical management system update for MAPPO and BCNA <table border="1" data-bbox="483 344 1365 554"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>Yes</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
Line of Business	PA Required in Medical Management System (Yes/No)											
BCBS	Yes											
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1.1	Effective Date: 10/06/2022	New policy										
1.0	Effective Date: 09/22/2022	UM medical management system update for BCBS and BCN <table border="1" data-bbox="483 716 1365 926"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	No	BCNA	No
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* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.