Effective November 1, 2018, refer to Palmetto Article A56141

BlueCross BlueShield of Alabama

Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Besponsa (inotuzumab ozogamicin)

Policy #:	678	Effective Date:	April 1, 2018
Category:	Pharmacology	Latest Review Date:	February 2018

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Inotuzumab ozogamicin is an antibody-drug conjugate (ADC) consisting of a monoclonal antibody targeting CD22, a protein found on the surface of mature B-cells in most cases of acute lymphoblastic leukemia (ALL). Inotuzumab ozogamicin also contains a cytotoxic agent of calicheamicin. This cytotoxic agent is released into the B-cells when inotuzumab ozogamicin attaches to the CD22 protein on the surface of mature B-cells.

Black box warnings: hepatotoxicity, including fatal and life-threatening veno-occlusive disease (VOD) (also known as sinusoidal obstruction syndrome) and increased risk of post hematopoietic stem cell transplant (HSCT) non-relapse mortality.

Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service prior to November 1, 2018:

Blue Advantage will treat **Besponsa™ (inotuzumab ozogamicin)** as a **covered benefit** for the treatment of adults with **acute lymphocytic leukemia** when all of the following criteria are met:

- Relapsed or refractory disease; **and**
- CD22+ B-cell acute lymphoblastic leukemia; **and**
- Current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

Blue Advantage will treat **Besponsa™ (inotuzumab ozogamicin)** as a **non-covered benefit** and as **investigational** when the criteria above are not met, and for all other indications, including, but not limited to:

- Use as first-line of therapy for ALL.
- Use in combination with other chemotherapy agents.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The American Cancer Society estimates about 5960 new cases of ALL and 1470 deaths in the United States for 2018. For adults with newly diagnosed B-cell ALL, current therapies are related to 60% to 90% complete remission rates. Many of these individuals will relapse and only about 30% to 50% will have disease-free survival lasting 3 or more years. Allogeneic stem cell

transplantation is the main objective after salvage therapy, and complete remission is a requirement for subsequent transplantation. Few adults with relapsed or refractory B-cell ALL continue to transplantation because of the low rates of complete remission linked to current chemotherapy treatments.

The safety and efficacy of Besponsa™ was evaluated in the INO-VATE ALL. This was a randomized, open-label, international, multicenter study in patients with relapsed or refractory ALL. Eligible patients were 18 ≥ years of age with Philadelphia chromosome- negative or positive relapsed or refractory B-cell precursor ALL. Patients had Eastern Cooperative Oncology Group (ECOG) performance scores ranging from 0 to 2, bone marrow involvements with ≥ 5% blasts, adequate liver function (total serum bilirubin ≤ 1.5 X ULN), and SCr ≤ 1.5 X ULN. Exclusion criteria included extramedullary relapse, Burkett's or mixed lineage leukemia, active central nervous system leukemia, prior chemotherapy within ≤ 2 weeks before randomization, prior monoclonal antibodies or prior allogeneic hematopoietic stem cell transplant or other anti-CD22 immunotherapy ≤ 4 months before randomization, peripheral lymphoblasts > 10,000 uL, known systemic vasculitides, primary or secondary immunodeficiency, current or chronic hepatitis B or C infection, unstable or severe uncontrolled medical conditions, concurrent active malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix or localized prostate cancer treated with radiation or surgery, LVEF less than 45%, active heart disease, QTcF > 470 msec, MI within 6 months of randomization, history of ventricular arrhythmia, history of chronic liver disease, history of hepatic veno-occlusive disease, live vaccines 6 weeks before randomization, uncontrolled current serious active infection, and previous allergic reaction to monoclonal antibodies . Patients received a total dose of 1.8 mg/m^2 of Besponsa™; on day 1 they would receive 0.8 mg and 0.5 mg on day 8 and 15. Cycle 1 was 21 days; the subsequent 5 cycles lasted 28 days. When a patient achieved complete remission (CR) or CR with incomplete hematologic recovery (CRi) , the dose on day 1 was reduced to 0.5 mg. Besponsa™ was compared to standard-therapy. The primary endpoint, CR+CRi, showed a statistically significant improvement (80.7% vs 29.4%, P<0.001). Besponsa™ had CR in 35.8% of patients for a median of 8 months, with 89.7% of patients being negative for minimal residual disease. Meanwhile, the standard of care arm had CR in 17.4% of patients for a median 4.9 months, with 31.6% of patients being negative for minimal residual disease. Hematologic adverse events were the most common during the trial. Febrile neutropenia was the most frequently reported serious adverse effect in both groups. Liver related adverse events were more common in the Besponsa™ group than in the standard of care group. Cases of veno-occlusive disease occurred for up to 2 years post randomization, and occurred more frequently in the Besponsa™ group (11% vs 1%).

Kantarjian and colleagues compared the outcomes of individuals with relapsed or refractory ALL treated with inotuzumab ozogamicin versus those treated with standard chemotherapy. In the open-label, two-group, randomized phase III trial, 218 adults (18 years of age or older) with relapsed or refractory, CD22-positive, Philadelphia chromosome (Ph)-positive or Ph-negative ALL were assigned to one of two groups (n=109 inotuzumab ozogamicin, n=109 standard therapy). In the standard therapy group, 13 subjects refused to start treatment and they were not included in the as-treated remission analysis population (n=109 inotuzumab ozogamicin, n=96 standard therapy). The rate of complete remission or complete remission with incomplete hematologic recovery was higher the in inotuzumab ozogamicin group than in the standard-

therapy group (80.7% [95% confidence interval {CI}, 72.1 to 87.7] vs. 33.3% [95% CI, 24.0 to 43.7], p<0.001). Within the group of subjects who reached complete remission or complete remission with incomplete hematologic recovery, the inotuzumab group had the higher percentage of bone marrow blast results below the threshold for minimal residual disease than the standard therapy group (78.4% [95% CI, 68.4 to 86.5] vs. 28.1% [95% CI, 13.7 to 46.7], p<0.001). More subjects in the inotuzumab ozogamicin group continued to stem cell transplantation right after treatment than in the standard therapy group (41% [45 of 109 subjects] vs. 11% [12 of 109 subjects], p<0.001). The intention-to-treat survival analysis included 164 subjects in the inotuzumab ozogamicin group and 162 subjects in the standard-therapy group. This analysis showed the progression-free survival was longer in the inotuzumab ozogamicin group than in the standard-therapy group (median, 5.0 months [95% CI, 3.7 to 5.6] vs. 1.8 months [95% CI, 1.5 to 2.2]; hazard ratio for disease progression, starting new induction therapy or stem cell transplantation without achieving complete remission, or death, 0.45 [97.5% CI, 0.34 to 0.61]; p<0.001). The potential of inotuzumab ozogamicin to increase the number of individuals capable to continue to stem cell transplantation after salvage therapy is encouraging.

The National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN CPG) for acute lymphoblastic leukemia (V5.2017) has a category 2A recommendation for inotuzumab ozogamicin when used as a treatment option for Ph-positive patients that are refractory/intolerant to TKIs and category 1 for Ph-negative patients.

Adverse Events
From the clinical trials data, the known adverse events with the use of inotuzumab ozogamicin were thrombocytopenia, grade 3 or higher febrile neutropenia, nausea, headache, pyrexia, and veno-occlusive disease. Kantarjian and colleagues reported adverse events pertaining to the liver were more common in the inotuzumab ozogamicin group than in the standard-therapy group. Subjects in the inotuzumab ozogamicin group received the trial drug at a starting dose of 1.8 mg/m^2. Veno-occlusive disease was noted more often in the inotuzumab ozogamicin group than in the standard therapy group (11% [15 individuals] vs. 1% [1 individual]). In the inotuzumab ozogamicin group, veno-occlusive disease occurred while the treatment was being given or shortly after in 5 individuals. After the trial, stem cell transplantation was performed in 48 subjects in the inotuzumab ozogamicin group, 10 of those subjects developed veno-occlusive disease post transplantation.

A weekly versus single-dose study reported that weekly inotuzumab ozogamicin is less toxic and as effective as single-dose inotuzumab ozogamicin. This study included 90 subjects with refractory or relapsed ALL. The individuals were separated into two schedule groups, weekly (n=41) and single-dose (n=49). The study showed 58% of participants reached bone marrow complete response and no change in response rate whether treatments were provided weekly or single dose. Liver function abnormalities and veno-occlusive disease were less common with the weekly schedule of inotuzumab ozogamicin.

Key Words:
Besponsa, ALL, acute lymphocytic leukemia, inotuzumab ozogamicin

Approved by Governing Bodies:

On August 17, 2017, the U.S. Food and Drug Administration (FDA) approved inotuzumab ozogamicin for the treatment of adults with relapsed or refractory B-cell precursor ALL. The FDA approval was based upon a randomized trial of 326 individuals with relapsed or refractory B-cell ALL who had previously undergone one or two previous treatments.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:	J9999	Not otherwise classified, antineoplastic drugs [when specified as inotuzumab ozogamicin (Besponsa)]

References:

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2. Besponsa™ Prescribing information. Pfizer. New York City, NY. August 2017.
3. Dang NH, Ogura M, Castaigne S, et al. Randomized, phase 3 trial of inotuzumab ozogamicin plus rituximab versus chemotherapy plus rituximab for relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. Br J Haematol. 2017.
4. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016; 375(8):740-753.
5. Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. Cancer. 2013; 119(15):2728-2736.
6. Mulhay N. FDA approves Inotuzumab Ozogamicin (Besponsa™) for ALL. Medscape. Available at:www.medscape.com/viewarticle/884434. Published August 17, 2017.
7. National Comprehensive Cancer Network® NCCN Clinical Practice Guidelines in OncologyTM. Available at: www.nccn.org/index.asp. Acute Lymphoblastic Leukemia (V5.2017). Revised October 27, 2017.
8. Reichert JM. Antibodies to watch in 2017. MAbs. 2017; 9(2):167-181.

Policy History:

Adopted for Blue Advantage, February 2018
Available for comment February 14, 2018 through March 31, 2018.
Medical Policy Group, November 2018

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.