POLICY NUMBER UM_1322	**SUBJECT** Besponsa™ (inotuzumab ozogamicin)		**DEPT/PROGRAM** UM Dept	**PAGE 1 OF 4**
DATE REVIEWED 09/13/17, 09/04/18, 08/08/19	**APPROVAL DATE** August 14, 2019	**EFFECTIVE DATE** August 14, 2019	**REVISION DATES** (latest version listed last) 08/14/19	
PRIMARY BUSINESS OWNER: **APPROVED BY:** Dr. Andrew Hertler		**COMMITTEE/BOARD APPROVAL** Utilization Management Committee		
URAC STANDARDS HUM 1		**ADDITIONAL AREAS OF IMPACT**		
CMS REQUIREMENTS	**STATE/FEDERAL REQUIREMENTS**		**APPLICABLE LINES OF BUSINESS** Oncology	

I. PURPOSE

To define and describe the accepted indications for Besponsa (inotuzumab ozogamicin) usage in the treatment of cancer.

II. DEFINITIONS

Besponsa (inotuzumab ozogamicin): is a CD22-directed antibody-drug conjugate (ADC) that has 3 components: the antibody inotuzumab, N-acetyl-gamma-calicheamicin dimethylhydrazide (a cytotoxic agent), and an acid-cleavable linker. Inotuzumab ozogamicin binds to CD22-expressing tumor cells, is internalized, and releases (via the linker) N-acetyl-gamma-calicheamicin dimethylhydrazide, thereby activating it to induce double-strand DNA breaks in the tumor cells. The result is cell cycle arrest and cell death.

Besponsa (inotuzumab ozogamicin) is FDA approved for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Besponsa (inotuzumab ozogamicin) is available in 0.9 mg intravenous powder for solution.

III. POLICY

New Century Health is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century Health may be deemed as not approvable and therefore not reimbursable. Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Besponsa (inotuzumab ozogamicin) may be considered medically necessary when any of the following selection criteria is met:

1. **Acute Lymphoblastic Leukemia (ALL)**
    a. The member has CD22 positive ALL and Besponsa (inotuzumab ozogamicin) is being used for the following criteria:
        i. For relapse/refractory Philadelphia chromosome-negative B-ALL after one or two previous induction chemotherapy regimens **OR**
        ii. For relapse/refractory Philadelphia chromosome-positive B-ALL after failure of one TKI and standard chemotherapy **AND**
        iii. Bone marrow blasts ≥ 5% **AND**
        iv. Total bilirubin level within normal limits.

Exclusion Criteria: Besponsa (inotuzumab ozogamicin) is not considered medically necessary when any of the following selection criteria is met:

1. Besponsa (inotuzumab ozogamicin) is being used after disease progression with the same regimen.
2. Hemopoietic stem cell transplant conditioning regimens contain dual alkylating agents (i.e. cyclophosphamide, carmustine, melphalan, busulfan, thiotepa).
3. Dosing exceeds single dose limit of Besponsa (inotuzumab ozogamicin) 0.8 mg/m^2.
4. Treatment exceeds the maximum duration limit of 6 cycles.
5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Besponsa (inotuzumab ozogamicin) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration**
    a. Prior to initiation (Patients with circulating lymphoblasts), give a combination of hydroxyurea, steroids, and/or vincristine to achieve cytoreduction to a peripheral blast count of 10,000/mm^3 or less before first dose
    b. Premedication, give a corticosteroid, antipyretic, and antihistamine
    c. First cycle, 0.8 mg/m^2 IV on day 1 and 0.5 mg/m^2 IV on days 8 and 15 for a total dose of 1.8 mg/m^2 per 3-week cycle; infuse over 1 hour at a rate of 50 mL/hr; may extend cycle to 4 week duration if complete remission (CR) achieved, complete remission with incomplete hematologic recovery (CRi) achieved, or if needed to allow recovery from toxicity
    d. Subsequent cycles (CR or CRi achieved), 0.5 mg/m^2 IV infusion over 1 hour at a rate of 50 mL/hr on days 1, 8, and 15 for a total dose of 1.5 mg/m^2 per 4-week cycle
    e. Subsequent cycles (CR or CRi not achieved), 0.8 mg/m^2 IV on day 1 and 0.5 mg/m^2 IV on days 8 and 15 for a total dose of 1.8 mg/m^2 per 4-week cycle
    f. Discontinue treatment if CR or CRi not achieved within 3 cycles
    g. Duration (Patients proceeding to hematopoietic stem cell transplant [HSCT]), 2 cycles; consider a third cycle if CR or CRi and minimal residual disease negativity are not achieved after 2 cycles
    h. Duration (Patients not proceeding to HSCT), maximum of 6 cycles.
2. **Dosage Adjustments:**
    a. Hepatic impairment (Total bilirubin 1.5 times ULN or less and AST/ALT 2.5 times ULN or less): No adjustment to starting dose required
    b. Geriatric: No adjustment required
    c. Hematologic toxicities (Absolute neutrophil count [ANC] 1 x 10^9/L or greater prior to treatment): If ANC decreases, do not interrupt current treatment cycle. Delay start of next treatment cycle until recovery of ANC to 1 x 10^9/L or greater. Discontinue treatment for persistently low ANC for longer than 28 days if treatment-related neutropenia is suspected.

d. Hematologic toxicities (Platelet count 50 x 10^9/L or greater prior to treatment): If platelet count decreases, do not interrupt current treatment cycle. Delay start of next treatment cycle until recovery of platelets to 50 x 10^9/L or greater. Discontinue treatment for persistently low platelet count for longer than 28 days if treatment-related neutropenia is suspected.

e. Hematologic toxicities (Neutropenia [ANC 1 x 10^9/L or lower] and/or thrombocytopenia [platelet count 50 x 10^9/L or lower)]) prior to treatment: If ANC or platelet count decreases, do not interrupt current treatment cycle. Delay start of next treatment cycle until one or more of the following criteria are met: ANC and platelet counts recover to baseline levels or higher for the prior cycle OR ANC recovers to 1 x 10^9/L or greater and platelet count recovers to 50 x 10^9/L or greater OR bone marrow assessment shows stable or improved disease and ANC and platelet count decrease is not considered to be treatment-related toxicity (effects are considered to be due to underlying disease).

f. Hepatic Tests (Total bilirubin greater than 1.5 times ULN and AST/ALT greater than 2.5 times ULN): Interrupt* current treatment. Do not administer a dose until recovery of total bilirubin to 1.5 x ULN or less and AST/ALT to 2.5 times ULN or less unless elevations are due to Gilbert's syndrome or hemolysis. If total bilirubin does not recover to 1.5 times ULN or less or if AST/ALT does not recover to 2.5 times ULN or less, permanently discontinue treatment. Permanently discontinue treatment for veno-occlusive disease (sinusoidal obstruction syndrome) or other severe liver toxicity.

g. Infusion related reactions: Interrupt* infusion and treat medically. Consider steroid or antihistamine treatment or discontinuation of infusion, depending on the severity of the reaction. Permanently discontinue treatment if a severe or life-threatening reaction occurs.

h. Non-hematologic toxicities (Grade 2 or greater): Interrupt* current treatment. Do not administer a dose until recovery to Grade 1 or pre-treatment grade level occurs.

i. Dosing Interruption: After a dosing interruption, modify doses according to the duration of the dose interruption (do not re-escalate the dose); less than 7 days (within a cycle), interrupt next dose and maintain a minimum of 6 days between doses; 7 days or more, omit the next dose within the cycle; 14 days or more, once adequate recovery is achieved, decrease the total dose for the next cycle by 25% and further reduce the number of doses per cycle to 2 in the subsequent cycle if necessary and consider discontinuation if reduction in dose and number of doses per cycle is not tolerated; greater than 28 days, consider permanent discontinuation.

3. **Monitoring**

a. Resolution or improvement of disease-related signs (reduction of blasts in the bone marrow and peripheral blood, recovery of blood counts, and resolution of extramedullary disease) may indicate efficacy.

b. Total bilirubin and liver function tests (LFTs): Prior to and following each dose; in patients proceeding to hemapoietic stem cell transplant (HSCT), monitor LFTs closely in the first month after HSCT, then according to standard medical practice.

c. Signs and symptoms of hepatic venoocclusive disease, including rapid weight gain, ascites, and hepatomegaly (possibly painful).

d. Toxicity, including signs and symptoms of hepatic venoocclusive disease and infection: Post-HSCT.

e. Signs and symptoms of infection, bleeding or hemorrhage, and other signs of myelosuppression: During therapy.

f. CBC: Prior to each dose.

g. Electrolytes and ECG: prior to the start of therapy, after initiation of any drug known to prolong the QTc interval, and periodically as clinically indicated during therapy.

h. Infusion related reactions (including symptoms such as fever, chills, rash, or breathing problems): During and for 1 hour following infusion.

V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

None

VII. REFERENCES

1. Besponsa PI prescribing information. Wyeth Pharmaceuticals Inc. Philadelphia, PA 2018.
2. Clinical Pharmacology Elsevier Gold Standard. 2019.
3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2019.
4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2019.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD. 2019.