Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Inotuzumab ozogamicin (Besponsa®)	MP-RX-FP-12-23	☒ MMM MA ☒ MMM MultiHealth	11/30/2023	03/24/2026
			Last Review Date: 03/24/2026	**Frequently Revision:** Annual

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of Inotuzumab ozogamicin (Besponsa®), a CD22-directed antibody and cytotoxic drug conjugate (ADC) approved by the Food and Drug Administration (FDA) for the treatment of adults and pediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL).

Background Information

Besponsa is an antibody-drug conjugate composed of a monoclonal antibody targeting CD22 and the cytotoxic agent calicheamicin, which is released into the malignant cells upon binding. It is used to treat acute lymphoblastic leukemia (ALL) and should only be used in CD22+ B-cell ALL due to its molecular target.

The FDA approved Besponsa for CD22+ B-cell precursor ALL based on a phase 3 study (Kantarjian 2017). Besponsa monotherapy was compared to investigator's choice of standard therapy for patients aged 18 years or older with relapsed or refractory, philadelphia chromosome (Ph)- positive or Ph-negative ALL. All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG) of ≤2. NCCN additionally recommends the use of Besponsa in combination with a tyrosine kinase inhibitor (bosutinib, dasatinib, imatinib, nilotinib, or ponatinib) or mini-hyper CVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine) with or without blinatumumab in the relapse/refractory setting. NCCN also recommends Besponsa as induction therapy for Philadelphia chromosome-negative disease in combination with mini-hyper CVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine). This induction regimen may be used with or without blinatumomab consolidation therapy.

In March 2024, the FDA approved Besponsa for pediatric patients aged 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL. This decision was based on Study WI203581 (NCT02981628), a multicenter, single-arm, open-label phase 2 trial in 53 children. The study demonstrated a 42% complete remission rate, with a high percentage of patients achieving minimal residual disease (MRD) negativity. The pediatric approval expands the therapeutic scope of Besponsa, offering a new treatment option for children with limited alternatives.

Besponsa has a black box warning for hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS). Risk of VOD was greater in patient who underwent hematopoietic stem cell transplant (HSCT) after Besponsa treatment; other risk factors include liver disease, increased age, later salvage lines, and a greater number of Besponsa treatment cycles. Besponsa should

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be permanently discontinued if VOD occurs. Besponsa also has a black box warning for increased risk of post-HSCT non-relapse mortality because day 100 post-HSCT mortality was higher in patients receiving Besponsa.

Definitions and Measures

- Line of Therapy:
  - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
  - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
  - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- Complete Response (CR): defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥ 100 × 109/L and absolute neutrophil counts [ANC] ≥ 1 × 109/L) and resolution of any extramedullary disease.
- Complete Response with incomplete Hematological Recovery (Cri) is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, incomplete recovery of peripheral blood counts (platelets < 100 × 109/L and/or ANC < 1 × 109/L) and resolution of any extramedullary disease.
- Minimal Residual Disease (MRD) negativity. Minimal Residual Disease (MRD) refers to the small number of cancer cells that may remain in a patient's body after treatment for a hematologic malignancy, such as leukemia or lymphoma. MRD testing is used to detect and quantify these residual cancer cells. MRD negativity means that the treatment has been successful in reducing the cancer cells to undetectable levels or very low levels. MRD negativity is often associated with a better prognosis and an increased likelihood of long-term remission or cure.

Approved Indications

A. Besponsa is indicated for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adult and pediatric patients 1 year and older.

Other Uses

B. See Background section above.

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9229	Injection, inotuzumab ozogamicin, 0.1 mg [Besponsa]

ICD-10	Description
C83.50–C83.59	Diffuse large B-cell lymphoma (DLBCL)
C91.00-C91.02	Acute lymphoblastic leukemia (ALL)
D46.A	Refractory cytopenia with multilineage dysplasia

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Inotuzumab ozogamicin (Besponsa®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of CD22+ B-cell acute lymphocytic leukemia (ALL); **AND**
ii. Individual meets all of the following:
    A. Relapsed or refractory disease; **AND**
    B. Individual is using Besponsa as (NCCN 1/2A):
        1. A single agent; **OR**
        2. In combination with a tyrosine kinase inhibitor (bosutinib, dasatinib, imatinib, nilotinib, or ponatinib) for for Philadelphia chromosome-positive B-ALL; **OR**
        3. In combination with mini-hyper CVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine) and with or without blinatumomab as consolidation therapy;

OR

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iii. Individual has a diagnosis of CD22+ B-cell acute lymphocytic leukemia (ALL) (NCCN 2A); **AND**

iv. Individual is using Besponsa as induction (frontline) therapy for Philadelphia chromosome-negative disease; **AND**

v. Individual is using Besponsa in combination with mini-hyper CVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine) and with or without blinatumomab as consolidation therapy.

B. Criteria For Continuation of Therapy

i. MMM considers subsequent cycles of Besponsa clinically appropriate when there is no evidence of unacceptable toxicity or disease progression, and the recommended maximum duration of therapy has not been exceeded. The following information should be submitted for reauthorization:

A. Documentation from the treating physician showing no progression of disease.

B. Documentation indicating whether the patient achieved CR or CRi (see Background section above for definitions).

C. In order to continue therapy safely and in alignment with the prescribing information, the following clinical monitoring and precautions must be addressed and documented as applicable:

1. Myelosuppression: Monitor complete blood counts regularly. Submit documentation indicating that the patient is being monitored for signs and symptoms of infection, bleeding/hemorrhage, or other myelosuppression-related effects, and that appropriate management is in place.
2. Infusion-related reactions: Documentation from the treating provider that the patient is being monitored for infusion reactions during and for at least 1 hour after the end of each infusion.
3. QT interval prolongation: Provide baseline and follow-up ECG and electrolyte monitoring data. Indicate whether any concomitant medications known to prolong the QT interval are being used and if additional monitoring is being performed accordingly.

ii. For patients proceeding to hematopoietic stem cell transplant (HSCT), the recommended duration of treatment with Besponsa is 2 cycles.

A. MMM considers a third cycle of Besponsa medically appropriate for patients who do not achieve CR or CRi and minimal residual disease (MRD) negativity after 2 cycles. In this setting, the following information should be submitted for reauthorization:

1. Documentation on whether the patient achieved CR or CRi.
2. Documentation on whether the patient achieved minimal residual disease (MRD) negativity after the first two 2 cycles.

iii. For all other patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be approved.

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A. In accordance with Besponsa's FDA approved labeling, MMM does not consider continuation of treatment with Besponsa medically appropriate in patients who fail to achieve a CR or CRi within 3 cycles.

C. Authorization Duration

i. Initial Approval Duration: Up to a maximum of 1 cycle (3-4 weeks)
ii. Reauthorization Approval Duration: Up to a maximum of 1 cycle (4 weeks)

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for Besponsa (inotuzumab ozogamicin) may not be approved if the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications not included above.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

i. Cycle 1 of the treatment regimen is designed to last for 3 weeks (21 days). However, it can be extended to 4 weeks (28 days) under specific circumstances:
   A. If the patient achieves Complete Remission (CR) or Complete Remission with incomplete hematologic recovery (CRi), an extension to a 4-week cycle is considered. In this case, treatment will be administered on Days 1, 8, and 15, with a 7-day treatment-free interval starting on Day 21.
   B. An extension to a 4-week cycle may also be warranted to allow for toxicity recovery. In this scenario, a 7-day treatment-free interval starting on Day 21 is recommended.

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ii. Subsequent treatment cycles have a duration of 4 weeks, with treatment administered on Days 1, 8, and 15, followed by a 7-day treatment-free interval starting on Day 21. Recommended dose depends on the patient's response to treatment.

iii. Discontinuation is recommended in patients who fail to achieve a CR or CRi within 3 cycles.

Drug: Besponsa injection (0.9 mg single-dose vial)			
	Day 1	Day 8	Day 15
Cycle 1			
Dose[a]	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	21 days. Can be extended to 28 days in patients who have achieved CR or CRi, and/or to allow for recovery from toxicity (7-day treatment-free interval starting on Day 21)		
Subsequent Cycles in Patients who achieve CR[b] or CRi[c]			
Dose[a]	0.5 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 days[d]		
Subsequent Cycles in Patients who have not achieved CR[b] or CRi[c]			
Dose[a]	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 days[d]		

[a] Dose is based on the patient's Body Surface Area (BSA).
[b] CR is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (platelets ≥ 100 × 109/L and absolute neutrophil counts [ANC] ≥ 1 × 109/L) and resolution of any extramedullary disease.
[c] CRi is defined as < 5% blasts in the bone marrow and the absence of peripheral blood leukemic blasts, incomplete recovery of peripheral blood counts (platelets < 100 × 109/L and/or ANC < 1 × 109/L) and resolution of any extramedullary disease.
[d] 7-day treatment-free interval starting on Day 21.

Exceptions

- The recommended duration of treatment is 2 cycles for patients proceeding to hematopoietic cell transplant (HCT); may consider a third cycle in patients who do not achieve CR or CRi and minimal residual disease (MRD) negativity after 2 cycles. For patients not proceeding to HSCT, may continue treatment for up to a maximum of 6 cycles.
- **Inotuzumab Ozogamicin Dose Modifications for Hematologic Toxicities**

Criteria	Inotuzumab ozogamicin dose modification(s)

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If prior to inotuzumab ozogamicin treatment ANC was ≥1,000/mm^3	If ANC decreases, then interrupt the next cycle of treatment until recovery of ANC to ≥1,000/mm^3. Discontinue inotuzumab ozogamicin if low ANC persists for >28 days and is suspected to be related to inotuzumab ozogamicin.
If prior to inotuzumab ozogamicin treatment platelet count was ≥50,000/mm^3 [a]	If platelet count decreases, then interrupt the next cycle of treatment until platelet count recovers to ≥50,000/mm^3. Discontinue inotuzumab ozogamicin if low platelet count persists for >28 days and is suspected to be related to inotuzumab ozogamicin.
If prior to inotuzumab ozogamicin treatment ANC was <1,000/mm^3 and/or platelet count was <50,000/mm^3 [a]	If ANC or platelet count decreases, then interrupt the next cycle of treatment until at least one of the following occurs: ANC and platelet counts recover to at least baseline levels for the prior cycle, **or** ANC recovers to ≥1,000/mm^3 and platelet count recovers to ≥50,000/mm^3, **or** stable or improved disease (based on most recent bone marrow assessment) and the ANC and platelet count decrease is considered to be due to the underlying disease (not considered to be inotuzumab ozogamicin-related toxicity).

[a] Platelet count used for dosage modification should be independent of transfusion.

- **Inotuzumab Ozogamicin Dose Modifications Depending on Duration of Dosing Interruption Due to Nonhematologic Toxicity**

Duration of dose interruption due to toxicity	Inotuzumab ozogamicin dose modification(s)
<7 days (within a cycle)	Interrupt the next dose (maintain a minimum of 6 days between doses).
≥7 days	Omit the next dose within the cycle.
≥14 days	Once adequate recovery is achieved, decrease the total dose by 25% for the subsequent cycle. If further dose modification is required, then reduce the number of doses to 2 per cycle for subsequent cycles. If a 25% decrease in the total dose followed by a decrease to 2 doses per cycle is not tolerated, then permanently discontinue treatment.
>28 days	Consider permanent discontinuation of treatment.

- **Inotuzumab Ozogamicin Dose Modifications for Nonhematologic Toxicities**

Nonhematologic toxicity	Inotuzumab ozogamicin dose modification(s)

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Bleeding/Hemorrhage	May require dosing interruption, dose reduction, or permanent discontinuation.
Hepatotoxicity	See "Dosage: Hepatic Function Impairment".
Infection (severe)	May require dosing interruption, dose reduction, or permanent discontinuation.
Infusion-related reaction	Interrupt the infusion and institute appropriate medical management. Depending on the severity of the infusion related reaction, consider discontinuation of the infusion or administration of corticosteroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue treatment.
Other nonhematologic toxicity ≥ grade 2	Interrupt treatment until recovery to grade 1 or pretreatment grade levels prior to each dose.

Reference Information

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2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. 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.
4. Kantarjian H, Ravandi F, Short NJ, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. Lancet Oncol 2018;19:240- 248.
5. Jabbour E, Ravindi F, Kebriaei P, et al. Salvage chemoinnunotherapy with inotuzumab ozogamicin combined with mini-Hyper-CVD for patients with relapsed or refractory Philadephia chromosome-negative acute lymphoblastic leukemia: A phase 2 clinical trial. JAMA oncol 2018; 4:230-234.
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7. NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on February 3, 2026.
    a. Pediatric Acute lymphoblastic Leukemia. V1.2026. Revised August 11, 2025.
    b. Acute Lymphoblastic Leukemia. V2.2025. Revised June 27, 2025.

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9. UpToDate, Inc. Inotuzumab ozogamicin: Drug information. Available at: https://www.uptodate.com/contents/inotuzumab-ozogamicin-drug-information?search=besponsa&source=panel_search_result&selectedTitle=1~12&usage_type=panel&kp_tab=drug_general&display_rank=1#F50546904. Accessed February 3, 2026.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Updated pharmacologic class description and specified indication for CD22 positive as well as approval for pediatric use. Updated Background Information to remove NCCN recommendation for pediatric use, added FDA approval for pediatric population in 2024. Coding Reviewed: added C83.50–C83.59. Expanded Continuation Criteria to include safety monitoring and precautions. Added dosage form and dose modifications for toxicities. Updated references. Wording and formatting changes.	3/17/2026	03/24/2026
Annual Review	Patient population has altered. No changes to criteria. Review of the information and it is up to date.	6/9/2025	6/19/2025
Annual review	Update combination with TKI to specify Philadelphia chromosome-positive disease; update frontline therapy to clarify it may be used with or without blinatumomab; Background section revised and updated; References updated; Dosing revised: no change; Coding Reviewed: No changes.	2/18/2025	3/6/2025
Focus Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023