Evolent Clinical Guideline 3061 for Besponsa™ (inotuzumab ozogamicin)

Guideline Number: Evolent_CG_3061	Applicable Codes	
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Original Date: December 2017	**Last Revised Date:** April 2026	**Implementation Date:** April 2026

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STATEMENT

Purpose

To define and describe the accepted indications for Besponsa (inotuzumab ozogamicin) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Acute Lymphoblastic Leukemia (ALL)

- Besponsa (inotuzumab ozogamicin) may be used in adult and pediatric members 1 year and older:
  - As a single agent for Philadelphia chromosome negative relapsed/refractory CD22-positive B cell ALL, or
  - In combination with a tyrosine kinase inhibitor (e.g., imatinib) for Philadelphia chromosome positive relapsed/refractory CD22-positive B cell ALL.

CONTRAINDICATIONS/WARNINGS

- Contraindications
  - None
- US Boxed Warning
  - Hepatotoxicity, including fatal and life-threatening veno-occlusive disease (VOD) occurred in patients with relapsed or refractory acute lymphoblastic leukemia (ALL)

who received inotuzumab ozogamicin. The risk of VOD was greater in patients who underwent hematopoietic stem cell transplant (HSCT) after inotuzumab ozogamicin treatment; use of HSCT conditioning regimens containing 2 alkylating agents and last total bilirubin level ≥ upper limit of normal (ULN) before HSCT were significantly associated with an increased risk of VOD.

- Other risk factors for VOD in patients treated with inotuzumab ozogamicin included ongoing or prior liver disease, prior HSCT, increased age, later salvage lines, and a greater number of inotuzumab ozogamicin treatment cycles.
- Elevation of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of inotuzumab ozogamicin. Permanently discontinue treatment if VOD occurs. If severe VOD occurs, treat according to standard medical practice.

- Increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality:
  - There was higher post-HSCT non-relapse mortality rate in patients receiving inotuzumab ozogamicin, resulting in a higher Day 100 post-HSCT mortality rate.

EXCLUSION CRITERIA

- Besponsa (inotuzumab ozogamicin) use after disease progression with the same regimen.
- Lack of documentation of CD-22 positivity on leukemia cells.
- Dosing exceeds single dose limit of Besponsa (inotuzumab ozogamicin) 0.8 mg/m^2.
- Treatment exceeds a total of 6 cycles (if hematopoietic stem cell transplant not planned).
- Investigational use of Besponsa (inotuzumab ozogamicin) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
  - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
  - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
  - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
  - Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).

- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J9229 - Injection, inotuzumab ozogamicin, 0.1 mg

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
April 2026	• Updated references
April 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1330 Besponsa (inotuzumab ozogamicin) • Updated references
April 2024	• Updated NCH verbiage to Evolent • Updated indication to include use in pediatric members ≥ 1 year

Date	Summary
	• Added new reference

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Kantarjian HM, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. *Cancer*. 2019 Jul 15;125(14):2474-2487. doi: 10.1002/cncr.32116.
2. Kantarjian HM, et al. INO-VATE ALL Clinical Trial. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N Engl J Med*. 2016 Aug 25;375(8):740-753. doi: 10.1056/NEJMoa1509277.
3. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inotuzumab-ozogamicin-pediatric-patients-acute-lymphoblastic-leukemia
4. Besponsa prescribing information. Wyeth Pharmaceuticals LLC. Philadelphia, PA 2024.
5. Clinical Pharmacology Elsevier Gold Standard 2026.
6. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2026.
7. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2026.

8. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2026.
9. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
10. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.
11. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

ADDENDUM

- For Superior Texas Medicaid members: when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid coverage provisions for Besponsa clinical policy.