Clinical Policy: Azacitidine (Onureg, Vidaza)

Reference Number: CP.PHAR.387
Effective Date: 12.01.18
Last Review Date: 11.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Azacitidine (Onureg®, Vidaza®) is a nucleoside metabolic inhibitor.

FDA Approved Indication(s)

Onureg is indicated for continued treatment of adult patients with acute myeloid leukemia (AML) who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

Vidaza is indicated for the treatment of:

- Adult patients with the following French-American-British (FAB) myelodysplastic syndrome (MDS) subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).
- Pediatric patients aged 1 month and older with newly diagnosed juvenile myelomonocytic leukemia (JMML).

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that azacitidine, Onureg, and Vidaza are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Myelodysplastic Syndromes (must meet all)**:**

1. Diagnosis of MDS, including JMML;
2. Request is for generic azacitidine or Vidaza;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. One of the following (a or b):
   a. Age ≥ 18 years;
   b. Age ≥ 1 month, and request is for JMML;
5. For brand Vidaza requests, member must use generic azacitidine, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a, b, or c):*
   a. For MDS, dose does not exceed one of the following (i or ii):

i. Initial: 75 mg/m^2 per day for 7 days;
ii. Maintenance: 100 mg/m^2 per day for 7 days per 4-week cycle;

b. For JMML, dose does not exceed one of the following administered daily for 7 days per 28-day cycle, for up to 6 cycles (i or ii):
i. Age 1 month to less than 1 year or weighing less than 10 kg: 2.5 mg/kg;
ii. Age 1 year and older and weighing 10 kg or greater: 75 mg/m^2;

c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Acute Myeloid Leukemia (Vidaza off-label) (must meet all)**:**

1. Diagnosis of AML;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For Onureg requests, all of the following (a, b, c, and d):
   a. Request is for maintenance therapy;
   b. Prescribed as a single agent;
   c. Member achieved CR or CRi following intensive induction chemotherapy (*see Appendix D*);
   d. One of the following (i or ii):*
      **For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395*
      i. Medical justification supports inability to use SC/IV azacitidine (e.g., contraindication to excipients);
      ii. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*);
5. For Vidaza requests, prescribed in one of the following ways (a-f):
   a. As a single agent;
   b. In combination with Venclexta®;
   c. For relapsed or refractory disease with FLT3-ITD (internal tandem duplication) mutation: In combination with Nexavar®;
   d. For IDH1 mutation: In combination with Tibsovo®;
   e. For IDH2 mutation: In combination with Idhifa®;
   f. For FLT3-ITD or TKD (tyrosine kinase domain) mutation in disease without IDH1 mutation: In combination with Xospata®;
6. For brand product requests, member must use generic azacitidine, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a, b, or c):*
   a. Onureg: Dose does not exceed 300 mg (1 tablet) per day for 14 days per 4-week cycle;
   b. Vidaza: Dose does not exceed 100 mg/m^2 per day for 7 days per 4-week cycle;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – Onureg: 6 months; Vidaza: 6 months or to the member's renewal date, whichever is longer

C. Myeloproliferative Neoplasms (off-label) (must meet all)**:**
1. Diagnosis of advanced phase (i.e., accelerated- or blast-phase) myeloproliferative neoplasms;
2. Request is for generic azacitidine or Vidaza;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age ≥ 18 years;
5. Prescribed as bridging therapy prior to transplant, unless member is not a candidate for transplant;
6. One of the following (a or b):
   a. Prescribed as a single agent or in combination with Jakafi®, Inrebic®, Ojjaara®, or Vonjo® for palliation of splenomegaly or other disease-related symptoms;
   b. Prescribed in combination with Venclexta;
7. For brand Vidaza requests, member must use generic azacitidine, unless contraindicated or clinically significant adverse effects are experienced;
8. Request meets one of the following (a or b):*
   a. Dose does not exceed 100 mg/m^2 per day for 7 days per 4-week cycle;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

D. Peripheral T-Cell Lymphoma (off-label) (must meet all)**:**
1. Diagnosis of one of the following peripheral T-cell lymphomas (a, b, or c):
   a. Angioimmunoblastic T-cell lymphoma;
   b. Nodal peripheral T-cell lymphoma with TFH phenotype;
   c. Follicular T-cell lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Disease is relapsed or refractory;
5. Prescribed as a single agent for one of the following (a or b):
   a. Initial palliative therapy;
   b. Second-line or subsequent therapy;
6. For Onureg requests, one of the following (a or b):*

   **For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395*

   a. Medical justification supports inability to use SC/IV azacitidine (e.g., contraindication to excipients);
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*);

7. For brand product requests, member must use generic azacitidine, if available, unless contraindicated or clinically significant adverse effects are experienced;
8. Request meets one of the following (a, b, or c):*
   a. Onureg: Dose does not exceed 300 mg (1 tablet) per day for 14 days per 4-week cycle;
   b. Vidaza: Dose does not exceed 100 mg/m^2 per day for 7 days per 4-week cycle;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – Onureg: 12 months; Vidaza: 6 months or to the member's renewal date, whichever is longer

E. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Vidaza or Onureg for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For brand product requests, member must use generic azacitidine, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, request meets one of the following (a, b, c, or d):*
   a. Onureg: New dose does not exceed 300 mg (1 tablet) per day for 14 days per 4-week cycle;
   b. Vidaza for MDS: New dose does not exceed 100 mg/m^2 per day for 7 days per 4-week cycle;

c. Vidaza for JMML: New dose does not exceed one of the following administered daily for 7 days per 28-day cycle, for up to 6 cycles (i or ii):
   i. Age 1 month to less than 1 year or weighing less than 10 kg: 2.5 mg/kg;
   ii. Age 1 year and older and weighing 10 kg or greater: 75 mg/m^2;
d. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – Onureg: 12 months; Vidaza: 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AML: acute myelogenous leukemia
ANC: absolute neutrophil count
CMMoL/CMML: chronic myelomonocytic leukemia
CR: complete response
CRi: complete response with incomplete hematologic recovery
FAB: French-American-British
FDA: Food and Drug Administration
ITD: internal tandem duplication
JMML: juvenile myelomonocytic leukemia
MDS: myelodysplastic syndrome
MF: myelofibrosis
NCCN: National Comprehensive Cancer Network

RA: refractory anemia
RAEB: refractory anemia with excess blasts
RAEB-T: refractory anemia with excess blasts in transformation
RARS: refractory anemia with ringed sideroblasts
TKD: tyrosine kinase domain

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings:
- Contraindication(s): advanced malignant hepatic tumors (Vidaza only), hypersensitivity to azacitidine (or mannitol for Vidaza only)
- Boxed warning(s): none reported

Appendix D: General Information
The National Comprehensive Cancer Network (NCCN) AML treatment guidelines define morphologic CR in patients that are independent of transfusions as follows:
- Absolute neutrophil count (ANC) > 1,000/mcL (blasts < 5%)
- Platelets ≥ 100,000/mcL (blasts < 5%)

NCCN presents CRi (a variant of CR) for AML as follows based on clinical trial information:
- < 5% marrow blasts
- Either ANC < 1,000/mcL or platelets < 100,000/mcL
- Transfusion independence but with persistence of neutropenia (< 1,000/mcL) or thrombocytopenia (< 100,000/mcL)

Appendix E: States with Regulations against Redirections in Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
IN	Yes	For advanced, metastatic cancer and associated conditions
LA	Yes[≠]	For stage 4 advanced, metastatic cancer or associated conditions. [≠]Exception if clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
MS	Yes	For advanced metastatic cancer and associated conditions
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	For stage 4 metastatic cancer and associated conditions
OK	Yes	For advanced metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer

State	Step Therapy Prohibited?	Notes
TN	Yes^	For stage 4 advanced metastatic cancer, metastatic blood cancer, and associated conditions ^Exception if step therapy is for AB-rated generic equivalent, interchangeable biological product, or biosimilar product to the equivalent brand drug
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Azacitidine (Onureg)	AML	300 mg PO QD on days 1 through 14 of each 28-day cycle	300 mg/day for 14 days/cycle
Azacitidine (Vidaza)	MDS	75 mg/m^2 SC or IV infusion QD for 7 days. Repeat cycle every 4 weeks. May increase to 100 mg/m^2 (after 2 treatment cycles). Patients should be treated for a minimum of 4 to 6 cycles. Doses may be adjusted or delayed based on hematology lab values, renal function, or serum electrolytes. Continue treatment as long as the patient continues to benefit	100 mg/m^2/day for 7 days/cycle
	JMML	Age 1 month to less than 1 year or weighing less than 10 kg: 2.5 mg/kg Age 1 year and older and weighing 10 kg or greater: 75 mg/m^2 Administer IV daily for 7 days in a 28-day cycle, for a minimum of 3 cycles and a maximum of 6 cycles	See dosing regimen

VI. Product Availability

Drug Name	Availability
Azacitidine (Onureg)	Tablets: 200 mg, 300 mg
Azacitidine (Vidaza)	Lyophilized powder in single dose vial: 100 mg

VII. References

1. Onureg Prescribing Information. Summit, NJ: Celgene Corporation; October 2022. Available at: https://onuregpro.com. Accessed July 11, 2025.
2. Vidaza Prescribing Information. Summit, NJ: Celgene Corporation; January 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/050794s036lbl.pdf. Accessed July 11, 2025.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed July 15, 2025.

4. National Comprehensive Cancer Network. Myelodysplastic Syndromes Version 2.2025. Available at http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed July 15, 2025.
5. National Comprehensive Cancer Network. Acute Myeloid Leukemia Version 2.2025. Available at http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed July 15, 2025.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9025	Injection, azacitidine, 1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2021 annual review: added criteria that Onureg be administered as single-agent therapy and option that member could decline consolidation/curative therapy for Onureg request per NCCN compendium; updated NCCN definition of CR and CRi in General Information and Appendix D; modified reference from HIM.PHAR.21 to HIM.PA.154; for Onureg requests, added requirement for use of generic if available; references reviewed and updated.	08.06.21	11.21
For AML, added redirection bypass for states with regulations against redirections in Stage IV or metastatic cancer along with additional information in Appendix E; for Onureg added allowance for continuation of care in Section II.	12.15.21	
RT4: added additional indication for Vidaza in pediatric patients aged 1 month and older with newly diagnosed JMML per updated prescribing information; generalized oncology redirection bypass language.	05.26.22	
4Q 2022 annual review: no significant changes; references reviewed and updated. Template changes applied to other diagnoses/indications.	08.01.22	11.22
Updated Appendix E to include Oklahoma.	06.07.23	
4Q 2023 annual review: no significant changes; references reviewed and updated.	06.30.23	11.23
Added Mississippi to Appendix E.	06.05.24	
4Q 2024 annual review: revised policy/criteria section to also include generic azacitidine; for all indications where applicable, updated generic redirection to include Vidaza; for AML, removed requirement for Onureg that member is not able to or declines to	08.08.24	11.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
complete intensive consolidation therapy and added requirements regarding usage of Vidaza (single agent and combination) per NCCN; updated off-label criteria for "myelofibrosis" to instead refer to "myeloproliferative neoplasms" and added specific requirements around recommended uses (bridging therapy prior to transplant and use as a single agent or in various combinations) per NCCN; added off-label criteria for peripheral T-cell lymphomas per NCCN; references reviewed and updated.		
4Q 2025 annual review: for AML, added that use with Nexavar must be for relapsed or refractory disease per NCCN; added step therapy bypass for IL HIM per IL HB 5395; extended initial approval durations from 6 to 12 months for HIM/Medicaid and for Onureg requests for Commercial; updated Appendix E with revised language and exception for Tennessee; references reviewed and updated.	07.15.25	11.25
For Appendix E, added state IN.	04.09.26	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan

retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For 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 manual for any coverage provisions pertaining to this clinical policy.