CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Azacitidine (Vidaza®)

Version: 1.0

EFFECTIVE DATE: 2/1/2025

NantHealth® | Eviti®

Please note the following:

Azacitidine (Vidaza®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within 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.

Azacitidine (Vidaza): Discussion

Azacitidine is in a class of medications called demethylation agents. It works by helping the bone marrow to produce normal blood cells and by killing abnormal cells in the bone marrow.[1] It comprises the cellular uptake, intracellular activation, incorporation into nucleic acids, and inhibition of DNA methyltransferases, which has catalytic activity, thereby inducing DNA hypomethylation.[2]

Common adverse reactions noted in adult patients receiving subcutaneous therapy include nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, and ecchymosis. The most common adverse reactions via the intravenous route include petechiae, rigors, weakness, and hypokalemia. In pediatric patients with juvenile myelomonocytic leukemia (JMML), the most common adverse reactions are pyrexia, rash, upper respiratory tract infection, and anemia.

Azacitidine is approved by the Food and Drug Administration (FDA) for myelodysplastic syndrome and juvenile myelomonocytic leukemia (JMML).[3]

The National Comprehensive Cancer Network (NCCN) endorses azacitidine for the following cancer types: acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasms, and T-cell lymphoma.[4,5,6,7]

Azacitidine: Definitions

- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

Azacitidine: Policy

Note: Coverage of azacitidine will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Azacitidine will be considered for coverage when the following criteria are met:

Acute Myeloid Leukemia

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent for maintenance therapy given orally in patients with non-core binding factor (CBF) disease who received prior intensive chemotherapy for one of the following:
   a) In remission
   b) Completed no consolidation or some consolidation
   c) With no allogeneic hematopoietic cell transplantation planned; OR
4. In combination with venetoclax for intensive induction treatment for one of the following:
   a) Therapy related to disease other than CBF-AML, antecedent MDS/CMML, or cytogenetic changes consistent with MDS (previously classified as AML-MRC)
   b) Poor-risk disease without TP53-mutation or del17p abnormality; OR
5. Single agent for one of the following:
   a) Lower-intensity treatment induction when not a candidate for intensive induction therapy or declines, and contraindication to venetoclax
   b) Follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
   c) Consolidation therapy as a continuation of the low-intensity regimen used for induction in patients with poor-risk MDS with and without TP53-mutation or del17p abnormality, therapy-related disease other than CBF-AML, antecedent MDS/CMML, or cytogenetic changes consistent with MDS (previously classified as AML-MRC)
   d) Maintenance therapy with non-CBF disease who received prior intensive chemotherapy for one of the following:
      i. In remission
      ii. Completed no consolidation or some consolidation
      iii. With no allogeneic hematopoietic cell transplantation planned
      iv. Unable to receive oral azacitidine; OR
6. In combination with venetoclax for one of the following:
   a) Lower-intensity treatment induction when not a candidate for intensive induction therapy or if patient declines
   b) Follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
   c) Consolidation therapy as continuation of low-intensity regimen used for induction in patients with poor-risk AML with and without TP53-mutation or del17p abnormality, therapy-related disease other than CBF-AML, antecedent MDS/CMML, or cytogenetic changes consistent with MDS (previously classified as AML-MRC); OR

7. In combination with ivosidenib in patients with IDH1 mutation for one of the following:
   a) Lower-intensity treatment induction when not a candidate for intensive induction therapy or the patient declines
   b) Follow-up after induction therapy, following a response to previous lower intensity therapy with the same regimen
   c) Consolidation therapy as a continuation of low-intensity regimen used for induction in patients with poor-risk AML with and without TP53-mutation or del17p abnormality, therapy-related disease other than CBF-AML, antecedent MDS/CMML, or cytogenetic changes consistent with MDS (previously classified as AML-MRC); OR
8. In combination with enasidenib in patients with IDH2-mutated AML for one of the following:
   a) Lower-intensity treatment induction when not a candidate for intensive induction therapy or if the patient declines and is not eligible for a preferred regimen
   b) Follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
   c) Consolidation therapy as continuation of a low-intensity regimen used for induction for poor-risk disease with and without TP53-mutation or del17p abnormality, therapy-related AML other than CBF-AML, antecedent MDS/CMML, or cytogenetic changes consistent with MDS (previously classified as AML-MRC); OR
9. In combination with gilteritinib in patients with FLT3-ITD or TKD AML without IDH1 mutation for one of the following:
   a) Lower-intensity treatment induction when not a candidate for intensive induction therapy or if the patient declines and not eligible for a preferred regimen
   b) Follow-up after induction therapy following a response to previous lower intensity therapy with the same regimen
   c) Consolidation therapy as a continuation of low-intensity regimen used for induction in patients with poor-risk AML with and without TP53-mutation or del17p abnormality, therapy-related AML other than CBF-AML, antecedent MDS/CMML, or cytogenetic changes consistent with MDS (previously classified as AML-MRC); OR
10. Relapsed/refractory disease for one of the following:
    a) Single agent for less intensive therapy
    b) In combination with venetoclax for less intensive therapy
    c) In combination with sorafenib for targeted therapy (FLT3-ITD mutation); OR
11. In combination with venetoclax for one of the following:
    a) Systemic disease treated with palliative intent (patients with low performance and/or nutritional status [i.e., serum albumin <3.2 g/dL, not a candidate for intensive remission therapy or tagraxofusp-erzs])
    b) Relapsed/refractory disease.[4]

Juvenile Myelomonocytic Leukemia

1. At least 1 month old; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Newly diagnosed disease.[3]

Myelodysplastic Syndromes

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Patients with the following 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)[3]; OR

For **NCCN** required criteria coverage:

4. Patients with lower risk disease for one of the following:
   a) Clinically relevant thrombocytopenia or neutropenia
   b) Clinically relevant thrombocytopenia or neutropenia following disease progression or no response to or relapse after immunosuppressive therapy (+/- eltrombopag)
   c) Symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts <15% (or ring sideroblasts <5% with an SF3B1 mutation), with serum erythropoietin >500 mU/mL, and a poor probability to respond to immunosuppressive therapy (IST); OR
5. Patients with lower risk disease associated with symptomatic anemia for one of the following:
   a) With del(5q), with or without one other cytogenetic abnormality (except those involving chromosome 7), following no response to or relapse after either lenalidomide or an erythropoiesis-stimulating agent (ESA) if poor probability to respond to IST
   b) With no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts <15% (or ring sideroblasts <5% with an SF3B1 mutation), with serum erythropoietin ≤500 mU/mL following no response to or relapse after either an ESA alone (despite adequate iron stores) or luspatercept-aamt, followed by no response to or relapse after either an ESA with or without lenalidomide or a granulocyte-colony stimulating factor (G-CSF), or to imetelstat, or to luspatercept-aamt
   c) With no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts <15% (or ring sideroblasts <5% with an SF3B1 mutation), with serum erythropoietin >500 mU/mL following no response or intolerance to or relapse after IST
   d) With no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation), with serum erythropoietin ≤500 mU/mL following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after either imetelstat, or to an ESA with or without a G-CSF if poor probability to respond to IST
   e) With no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation), with serum erythropoietin >500 mU/mL following no response to or relapse after luspatercept-aamt followed by no response to or relapse after either lenalidomide or imetelstat if poor probability to respond to IST
   f) With no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation) following no response to or

relapse after imetelstat followed by no response to or relapse after either lenalidomide or luspatercept-aamt if poor probability to respond to IST; OR

6. Patients with lower risk disease associated with symptomatic anemia for one of the following:
   a) With del(5q), with or without one other cytogenetic abnormality (except those involving chromosome 7), following no response to or relapse after either lenalidomide or an erythropoiesis-stimulating agent (ESA), followed by no response to or intolerance or relapse after immunosuppressive therapy (IST)
   b) With no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation), with serum erythropoietin ≤500 mu/ml following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after either imetelstat, or to an ESA with or without G-CSF, followed by no response to or intolerance or relapse after IST
   c) With no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation), with serum erythropoietin >500 mU/mL following no response to or relapse after luspatercept-aamt followed by no response to or relapse after either lenalidomide or imetelstat followed by no response to or intolerance or relapse after IST
   d) With no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation) following no response to or relapse after imetelstat, followed by no response to or relapse after either lenalidomide or luspatercept-aamt, followed by no response to or intolerance or relapse after IST; OR
7. Patients with higher risk disease in transplant candidates for one of the following:
   a) Initial treatment in combination with either ivosidenib or olutasidenib if mIDH1 followed by allogeneic hematopoietic cell transplant (allo-HCT)
   b) Initial treatment as a single agent or in combination with venetoclax followed by allo-HCT
   c) In combination with olutasidenib followed by allo-HCT if mIDHI1 and no response to initial treatment with either azacitidine +/- venetoclax, decitabine +/- venetoclax, or high-intensity chemotherapy
   d) Single agent following relapse to or no response after allo-HCT
   e) Single agent as maintenance therapy if there is clinical benefit following treatment with the same agent; OR
8. Patients with higher risk disease in nontransplant candidates for one of the following:
   a) Single agent or in combination with venetoclax as initial treatment
   b) In combination with either ivosidenib or olutasidenib as initial treatment if mIDH1; OR
9. Treatment for one of the following:
   a) Single agent for chronic myelomonocytic leukemia CMML-1
   b) Single agent or in combination with venetoclax for CMML-2
   c) In combination with ruxolitinib for CMML-2 for symptom management or splenomegaly
   d) Single agent for MDS/MPN with neutrophilia
   e) In combination with ruxolitinib for MDS/MPN with neutrophilia with CSF3R or JAK2 mutations
   f) Single agent not otherwise specified for MDS/MPN
   g) Single agent or in combination with lenalidomide for MDS/MPN with SF3B1 mutation and thrombocytosis.[5]

Myeloproliferative Neoplasms - Accelerated/Blast Phase

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent or in combination with ruxolitinib, fedratinib, momelotinib, or pacritinib for palliation of splenomegaly or other disease-related symptoms for one of the following:
   a) Bridging therapy prior to the transplant
   b) If not a candidate for transplant; OR
4. In combination with venetoclax for the management of disease progression for one of the following:
   a) Bridging therapy prior to the transplant
   b) If not, a candidate for transplant.[6]

T- Cell Lymphomas/Peripheral T-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent second-line and subsequent therapy or initial palliative intent therapy for relapsed/refractory peripheral T-cell lymphomas [angioimmunoblastic T-cell lymphoma (AITL), nodal peripheral T-cell lymphoma (PTCL), T follicular helper (TFH) lymphoma, and follicular T-cell lymphoma (FTCL)].[7]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Azacitidine: References

1. National Library of Medicine (NIH). MedlinePlus. Azacitidine Injection. https://medlineplus.gov/druginfo/meds/a607068.html#:~:text=Azacitidine%20is%20used%20to%20treat,cells%20in%20the%20bone%20marrow. Accessed February 20, 2025.
2. Stomper Julia et al. Hypomethylating agents (HMA) for the treatment of acute myeloid leukemia and myelodysplastic syndromes: mechanisms of resistance and novel HMA-based therapies. https://www.nature.com/articles/s41375-021-01218-0. Accessed February 20, 2025.

3. Azacitidine. Package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/050794s036lbl.pdf. Accessed February 20, 2025.
4. National Comprehensive Cancer Network. Acute Myeloid Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed February 20, 2025.
5. National Comprehensive Cancer Network. Myelodysplastic Syndromes. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed February 20, 2025.
6. National Comprehensive Cancer Network. Myeloproliferative Neoplasms. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed February 20, 2025.
7. National Comprehensive Cancer Network. T-Cell Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed February 20, 2025.

Azacitidine: Coding (CPT®, ICD 10, and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C84.4	Peripheral T-cell lymphomas
C92.0	Acute myeloid leukemia
C93.1	Chronic myelomonocytic leukemia
C93.3	Juvenile myelomonocytic leukemia
D47.1	Accelerated/blast phase myeloproliferative neoplasms
D64.9	Myelodysplastic syndrome
J9025	Azacitidine

Azacitidine: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	2/1/2025
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	2/25/2025
6	Revision Changes:	