Medical Drug Clinical Criteria

Subject:	Vidaza (azacitidine)		
Document #:	CC-0097	**Publish Date:**	04/01/2025
Status:	Revised	**Last Review Date:**	02/21/2025

Table of Contents

Overview

This document addresses the use of Vidaza (azacitidine). Vidaza is a nucleoside metabolic inhibitor used for treatment of myelodysplastic syndrome (MDS), juvenile myelomonocytic leukemia (JMML), and acute myelogenous leukemia (AML) under specific conditions.

In 2004, Vidaza was FDA approved to treat French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (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). Since the initial trials of Vidaza for MDS, new classification systems, such as World Health Organization (WHO) diagnostic criteria and the International Prognostic Scoring System and response criteria guidelines have been developed and revised. As a result, many of the patients in studies for MDS met criteria for having AML, validating the use of this agent in AML under certain conditions.

Vidaza is also indicated in combination with Tibsovo (ivosidenib) for the treatment of newly diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy

Vidaza is also FDA indicated for newly diagnosed JMML in those aged one month and older.

The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Vidaza in AML. These include the following:

- Used in combination with venetoclax in patients* for induction treatment in candidates for intensive induction therapy 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 (AML-MRC)

- Used as a single agent in patients* for
  - low-intensity treatment induction in candidates for intensive induction therapy 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 (AML-MRC) (NCCN 2B)
  - low-intensity treatment induction when not a candidate for intensive induction therapy
  - follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
  - consolidation therapy as continuation of low-intensity regimen used for induction in patients age <60 and ≥60 years 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 (AML-MRC)
  - maintenance therapy in patients with intermediate or adverse risk disease who received prior intensive chemotherapy and whose disease is now in remission, completed no consolidation, some consolidation or are recommended to receive a course of consolidation, and with no allogeneic hematopoietic cell transplantation planned

- Used in combination with sorafenib in patients* with FLT3-ITD mutation for
  - low-intensity treatment induction when not a candidate for intensive induction therapy
  - follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
  - consolidation therapy as continuation of low-intensity regimen used for induction in patients age <60 and ≥60 years 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 (AML-MRC)

- Used in combination with venetoclax in patients* for
  - low-intensity treatment induction when not a candidate for intensive induction therapy (preferred)
  - follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
  - consolidation therapy as continuation of low-intensity regimen used for induction in patients age <60 and ≥60 years 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 (AML-MRC)

*Patients whose disease has progressed to AML from MDS after significant exposure to hypomethylating agents (HMAs) may be less likely to derive benefit from continued treatment with HMAs compared to patients who are HMA-naive. Alternative treatment strategies should be considered.

- Used in combination with ivosidenib in patients with IDH1 mutation for
  - low-intensity treatment induction when not a candidate for intensive induction therapy
  - follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
  - consolidation therapy as continuation of low-intensity regimen used for induction in patients age <60 and ≥60 years 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 (AML-MRC)

- Used in combination with enasidenib* in patients with IDH2-mutated AML for
  - lower-intensity treatment induction when not a candidate for intensive induction therapy or declines and not eligible for preferred regimen (useful in certain circumstances)
  - follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
  - 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 AML other than CBF-AML, antecedent MDS/CMML, or cytogenetic changes consistent with MDS (previously classified as AML-MRC)

- Used in combination with enasidenib* in patients with IDH2-mutated AML for
  - lower-intensity treatment induction when not a candidate for intensive induction therapy or declines and not eligible for preferred regimen (useful in certain circumstances)
  - follow-up after induction therapy following response to previous lower intensity therapy with the same regimen
  - 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 AML other than CBF-AML, antecedent MDS/CMML, or cytogenetic changes consistent with MDS (previously classified as AML-MRC)

  - For relapsed/refractory disease
    - as a component of repeating the initial successful induction regimen if ≥12 months since induction regimen
    - as a single agent (less aggressive therapy)
    - in combination with venetoclax (less aggressive therapy)
    - in combination with sorafenib (FLT3-ITD mutation)

  - Used in combination with venetoclax for Blastic Plasmacytoid Dendtritic Cell Neoplasm (BPDCN)
- systemic disease treated with palliative intent (patients with low performance and/or nutritional status (ie, serum albumin <3.2 g/dL; not a candidate for intensive remission therapy or tagraxofusp-erzs)
- relapsed/refractory disease

NCCN provides additional recommendations with a category 2A level of evidence for the use of Vidaza in Myeloproliferative Neoplasms. At this time the Myeloproliferative neoplasm guidelines only provide case reports for this use and the panel states there is very little data regarding the use of azacitidine or decitabine with fedratinib, momelotinib, or pacritinib for myelofibrosis in the accelerated phase or blast phase. The recommendation is suggested for clinical trials.

NCCN also provides additional recommendations with a category 2A level of evidence for the use of Vidaza in Peripheral T-cell lymphomas. NCCN guidelines for T-cell lymphomas suggested HDAC inhibitors may have superior activity in Peripheral T-cell lymphomas (PTCL) with TFH phenotype compared with non-TFH PTCL.(Falchi 2021, Ruan 2020). The Dupois 2022 abstract shares data from the ORACLE study with oral azacitidine in those with relapsed/refractory angioimmunoblastic T-cell lymphoma or nodal follicular helper T-cell lymphoma. Those treated with oral azacitidine had a longer median progression free survival than those treated with gemcitabine, bendamustine or romidepsin (5.6 months vs. 2.8 months). This did not reach statistical significance; however, the predetermined level was aggressive. Oral azacitidine (Onureg) was much better tolerated than the comparator arm. This data is extrapolated to the subcutaneous/intravenous formulation of azacitidine (Vidaza).

Definitions and Measures

Myelodysplastic syndrome (MDS): A condition that occurs when the blood-forming cells in the bone marrow are damaged.

- Primary MDS: Initial MDS diagnosis, usually when a cause is unknown.
- Secondary MDS: When a cause for the disease is known. Common causes include earlier treatment for a cancer; also known as treatment-related MDS.

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Clinical Criteria

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.

Vidaza (azacitidine)

Requests for Vidaza (azacitidine) may be approved if the following criteria are met:

I. Individual has a diagnosis of myelodysplastic syndrome (MDS) (Label, NCCN 1, 2A);

OR

II. Individual has a diagnosis of newly diagnosed juvenile myelomonocytic leukemia (JMML) (Label); **AND**
   A. Individual is at least one month and older;

OR

III. Individual has a diagnosis of acute myelogenous leukemia (AML), and one of the following are met:
   A. Azacitidine is used as a single agent for individuals 18 years of age and older or individuals who cannot tolerate more aggressive regimens (NCCN 2A); **OR**
   B. Azacitidine is used in combination with venetoclax for individuals 18 years of age and older or individuals who cannot tolerate more aggressive regimens (NCCN 1, 2A, DiNardo 2019, DiNardo 2020); **OR**
   C. Azacitidine is used in combination with venetoclax for individuals who are candidates for intensive induction therapy with poor risk AML (NCCN 2A); **OR**
   D. Azacitidine is used in combination with venetoclax for Blastic Plasmacytoid Dendritic Neoplasm (BPDCN) in systemic disease treated with palliative intent or relapsed/refractory disease (NCCN 2A); **OR**
   E. Azacitidine is used in combination with sorafenib for relapsed or refractory AML with FLT3-ITD mutations (NCCN 2A); **OR**
   F. Azacitidine is used in combination with ivosidenib (Tibsovo) for newly diagnosed AML with a susceptible IDH1 (isocitrate dehydrogenase-1) mutation in adults 60 years of age or older, or who have comorbidities that preclude use of intensive induction chemotherapy (which includes at least one of the following: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, creatinine clearance < 45 mL/min, or other comorbidity) (Tibsovo Label, NCCN 1); **OR**
   G. Azacitidine is used in combination with enasidenib (Idhifa) with IDH2-mutated AML for lower intensity treatment induction, follow-up after induction therapy following response to previous lower intensity therapy with the same regimen, or consolidation therapy as continuation of low-intensity regimen used for induction (NCCN 2A); **OR**
   H. Azacitidine is used in combination with gilteritinib (Xospata) with FLT3-ITD or TKD AML without IDH1 mutation for lower intensity treatment induction, follow-up after induction therapy following response to previous lower intensity therapy with the same regimen, or consolidation therapy as continuation of low-intensity regimen used for induction (NCCN 2A);
   I. Individual has AML arising from MDS;

OR

IV. Individual has a diagnosis of Peripheral T-cell lymphomas (including angioimmunoblastic T-cell lymphoma (AITL), nodal peripheral T-cell lymphoma with TFH phenotype (PTCL, TFH), and follicular T-cell lymphoma (FTCL) (NCCN 2A); **AND**
   A. Individual is using as second-line and subsequent therapy for relapsed/refractory disease; **AND**
   B. Azacitidine is used as a single agent;

OR

V. Individual has a diagnosis of myelofibrosis (MF) and one of the following are met (NCCN 2A):
   A. Azacitidine is used in combination with venetoclax for the management of disease progression of myeloproliferative neoplasms; **OR**

B. Azacitidine is used with or without ruxolitinib, fedratinib, momelotinib, or pacritinib in MF-accelerated/blast phase for palliation of splenomegaly or other disease related symptoms.
.

Requests for Vidaza (azacitidine) may not be approved for the following:

I. Individual has advanced malignant hepatic tumors; **OR**
II. When the above criteria are not met or for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9025	Injection, azacitidine, 1 mg [Vidaza]

ICD-10 Diagnosis

C84.40-C84.49	Peripheral T-cell lymphoma, not elsewhere classified
C86.40	Blastic NK-cell lymphoma not having achieved remission
C86.50	Angioimmunoblastic T-cell lymphoma not having achieved remission
C92.00-C92.02	Acute myeloblastic leukemia
C92.20-C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative
C92.40-C92.42	Acute promyelocytic leukemia
C92.50-C92.52	Acute myelomonocytic leukemia
C92.60-C92.62	Acute myeloid leukemia with 11q23-abnormality
C92.A0-C92.A2	Acute myeloid leukemia with multilineage dysplasia
C93.00-C93.02	Acute monoblastic/monocytic leukemia
C93.10-C93.12	Chronic myelomonocytic leukemia
C93.00-C93.02	Acute monoblastic/monocytic leukemia
C93.10-C93.12	Chronic myelomonocytic leukemia
C93.30-C93.32	Juvenile myelomonocytic leukemia
C94.00-C94.02	Acute erythroid leukemia
C94.40-C94.42	Acute panmyelosis with myelofibrosis
C94.6	Myelodysplastic disease, not classified
D46.0-D46.9	Myelodysplastic syndromes
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D75.81	Myelofibrosis

Document History

Revised: 02/21/2025
Document History:

- 02/21/2025 – Annual Review: Update existing criteria for use in AML due to NCCN 2A recommendations for use in combination with enasidenib with IDH2-mutated AML. Also add 2A recommendation for use in combination with gilteritinib in those with FLT3-ITD or TKD AML without IDH1 mutation. Coding Reviewed: Consolidated ICD-10-CM C93.30-C93.32 into one code range and updated description. Consolidated D46.0-C46.9 into one code range and updated description. Added ICD-10-CM C84.40-C84.49, C86.40, C86.50, C92.20-C92.22.
- 02/23/2024 – Annual Review: Update existing criteria for use in AML due to NCCN category 2A recommendations when used in combination with venetoclax, Add NCCN category 2A recommendation for use in Peripheral T-cell Lymphomas as second-line and subsequent therapy in relapsed/refractory disease. Update existing criteria for use in Myelofibrosis with

the addition of NCCN category 2A recommendation for use with venetoclax for the management of disease progression and use in MF-accelerated/blast phase. Wording and formatting updates. Coding Reviewed: No changes.
- 02/24/2023 – Annual: Add NCCN 2A criteria for use in Myelofibrosis. Minor wording and formatting updates. Coding Reviewed: No changes.
- 09/12/2022 – Select Review: Add criteria for use in newly diagnosed Juvenile Myelomonocytic Leukemia in those 1 month or older. Coding Reviewed: Added ICD-10-CM C93.30, C93.31, C93.32.
- 08/19/2022 – Select Review: Update combination use with Tibsovo and Venclexta for AML to include minimum age of 60 per NCCN; allow combination use with Venclexta for those with unfavorable risk genetics per NCCN. Coding reviewed: No changes.
- 06/13/2022 – Select Review: Add FDA approval for combination use with Tibsovo for the treatment of newly diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Add may not be approved criteria. Coding Reviewed: No Changes.
- 02/25/2022 – Annual Review: Add references to criteria. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: No changes. Coding reviewed: No changes.
- 02/21/2019 – Annual Review: No changes. Coding Reviewed: No changes.
- 05/17/2019 – Annual Review: First review of Vidaza clinical criteria. Add references for off label criteria. Add use in combination with venetoclax for older patients with relapsed or refractory AML. Coding Reviewed: No changes.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
2. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. Blood 2019;133:7-17
3. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl. J Med 2020; 383:617-629.
4. Dupuis J, Tsukasaki K, Bachy E, et al. Oral azacytidine in patients with relapsed/refractory angioimmunoblastic T-cell lymphoma: Final analysis of the Oracle phase III study [abstract]. Blood 2022;140(suppl 1):2310-2312.
5. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
6. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
7. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 18, 2024.
    a. Acute Myeloid Leukemia. V1.2025. Revised December 20, 2024.
    b. Myelodysplastic Syndromes. V2.2025 Revised January 17, 2025.
    c. Myeloproliferative Neoplasms. V2.2024. Revised August 8, 2024.
    d. T-cell Lymphomas. V1.2025. Revised November 11, 2024.
8. Ruan J, Moskowitz AJ, Mehta-Shah N, et al. Multi-Center Phase II Study of Oral Azacitidine (CC-486) Plus CHOP As Initial Treatment for Peripheral T-Cell Lymphoma (PTCL) [abstract]. Blood 2020;136:33-34. Available at: https://doi.org/10.1182/blood-2020-136023.

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.