09-J0000-84

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Reviewed: 12/08/21

Revised: 06/01/26

Subject: Azacitidine (Vidaza®) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Azacitidine (Vidaza®) is a pyrimidine nucleoside analog of cytidine (nucleoside metabolic inhibitor). Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. Azacitidine is used for the treatment of myelodysplastic syndrome (MDS) and is designated an orphan drug by the US Food and Drug Administration (FDA) for use in this condition. The drug is indicated for use in individuals with the following French-American-British (FAB) subtypes of MDS: refractory anemia (RA) or RA with ringed sideroblasts (RARS) if requiring blood transfusions or accompanied by neutropenia or thrombocytopenia, RA with excess blasts (RAEB), RAEB in transformation (RAEB-T) and chronic myelomonocytic leukemia (CMMoL).

Because MDS affects the bone marrow, it is staged differently than other types of cancer. There are various classification systems used to stage MDS including the International Prognostic Scoring System (IPSS), the Revised International Prognostic Scoring System (IPSS-R), and the World Health Organization (WHO) based prognostic scoring system (WPSS). The IPSS evaluates three components when determining an overall score of 0 to 2.5: percent marrow blasts, cytogenetics (e.g., del(5)q chromosome), and cytopenias. An IPSS score of 0 corresponds to low risk, 0.5-1 to intermediate risk 1, 1.5-2 to intermediate risk 2, and 2.5 or greater to high risk. The IPSS-R stratifies individuals into 1 of 5 risk groups and is a revised version of the IPSS. The IPSS-R includes more detailed cytogenetic subgroups, separate subgroups of the percent marrow blasts, and defined measurements for hemoglobin, platelets, and neutrophil counts. The WPSS assigns individuals to 1 of 5 risk groups, and risk category may change over the course of the disease. The system is based on the WHO subtype of MDS, karyotype, and severity of anemia and individuals fall into one of the following risk groups: very low, low, intermediate, high, and very high.

Although azacitidine is not a cure for MDS, use of the drug in combination with supportive care has been shown to be superior to use of supportive care alone in improving hematologic deficits (e.g., transfusion dependence) in individuals with MDS. In individuals with high-risk MDS, improved response rates and improved survival have been reported with azacitidine therapy compared with conventional care. National Comprehensive Cancer Network Clinical Practice Guidelines for MDS indicate that all individuals with MDS should receive relevant supportive care and recommend that additional treatment is based on stratification according to clinically significant cytopenia(s) into two major risk groups: 1) relative lower-risk individuals and 2) higher-risk individuals. Those deemed lower risk have a low or intermediate-1 category

International Prognostic Scoring System (IPSS), Revised International Prognostic Scoring System (IPSS-R) very low, low, or intermediate category, or WHO-classification based prognostic scoring system (WPSS) very low, low, or intermediate category. Individuals classified as high risk has an Intermediate-2/High IPSS, intermediate, high, or very high IPSS-R, or WPSS high or very high category. IPSS-R intermediate patients may be managed as very low/low risk or high/very high risk depending on additional prognostic factors such as age, performance status, serum ferritin levels, and serum lactate dehydrogenase (LDH) levels. Lower risk individuals can be further stratified according to chromosomal abnormalities and anemia characteristics. The NCCN guidelines also support the use of azacitidine for acute myelogenous leukemia and myeloproliferative neoplasms.

POSITION STATEMENT:

Drug Waste Reduction: Additional medical necessity criteria for dose optimization may apply depending on the requested dose and member's benefit. Refer to Medical Coverage Guideline Drug Waste Reduction, 09-J5000-54.

I. Initiation of azacitidine (Vidaza®) **meets the definition of medical necessity** when the dose does not exceed 100 mg/m2 per day and is administered for **ONE** of the following indications:

1. Acute Myeloid Leukemia (AML)
2. Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)
3. Myelodysplastic Syndrome (MDS)
4. Myelofibrosis (MF)
5. Myelodysplastic/Myeloproliferative (MDS/MPN) Overlap neoplasms (Chronic myelomonocytic leukemia subtype 1 (CMML-1), Chronic myelomonocytic leukemia subtype 2 (CMML-2), BCR-ABL negative atypical chronic myeloid leukemia, MDS/MPN overlap syndrome, MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
6. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
7. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

Approval duration: 1 year

II.Continuation of azacitidine (Vidaza®) **meets the definition of medical necessity** for the treatment of AML, BPDCN, MDS, MF, MDS/MPN Overlap neoplasms or other FDA-approved or NCCN diagnosis, when the following criteria are met:

A. The member has experienced a beneficial response to treatment

B. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member has previously met all indication-specific criteria for coverage

C. The dose does not exceed 100 mg/m^2 per day

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND

OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved:

- The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology values, is azacitidine 75 mg/m2 daily for 7 days to be administered by subcutaneous (SC) injection or intravenous (IV) infusion. Premedicate for nausea and vomiting.
- Repeat cycles every 4 weeks. After 2 cycles, may increase dose to 100 mg/m2 if no beneficial effect is seen and no toxicity other than nausea and vomiting has occurred. Patients should be treated for a minimum of 4 to 6 cycles. Complete or partial response may require additional treatment cycles
- Continue treatment as long as the patient continues to benefit

Dose Adjustments:

- Monitor patients for hematologic response and for renal toxicity; delay or reduce dosage as appropriate

Drug Availability: Azacitidine is supplied as a 100 mg single-use vial.

PRECAUTIONS:

CONTRAINDICATION

- Advanced malignant hepatic tumors
- Hypersensitivity to azacitidine or mannitol

WARNINGS AND PRECAUTIONS

- Anemia, neutropenia and thrombocytopenia: Monitor complete blood counts frequently (CBC)
- Hepatotoxicity: Patients with severe preexisting hepatic impairment are at higher risk for toxicity
- Renal impairment: Monitor patients with renal impairment for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys
- Monitor liver chemistries and serum creatinine prior to initiation of therapy and with each cycle
- Tumor lysis syndrome: fatalities have occurred. Assess baseline risk and monitor and treat as appropriate
- Azacitidine may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be apprised of the potential hazard to a fetus
- Men should be advised not to father a child during treatment.

BILLING/CODING INFORMATION:

HCPCS Coding:

J9025	Injection, Azacitidine, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

C86.4	Blastic NK-cell lymphoma
C92.00 – C92.02	Acute myeloblastic leukemia
C92.10 – C92.12	Chronic myeloid leukemia, BCR/ABL-positive

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
C92.90 – C92.92	Myeloid leukemia, unspecified
C92.A0 – C92.A2	Acute myeloid leukemia with multilineage dysplasia
C92.Z0 – C92.Z2	Other myeloid leukemia
C93.00 – C93.02	Acute monoblastic/monocytic leukemia
C93.10 – C93.12	Chronic myelomonocytic leukemia
C93.90 – C93.92	Monocytic leukemia, unspecified
C94.00 – C94.02	Acute erythroid leukemia
C94.20 – C94.22	Acute megakaryoblastic leukemia
C94.40 – C94.42	Acute panmyelosis with myelofibrosis
C94.6	Myelodysplastic disease, not classified
D46.0	Refractory anemia without ring sideroblasts, so stated
D46.1	Refractory anemia with ring sideroblasts
D46.20 – D46.22	Refractory anemia with excess of blasts
D46.4	Refractory anemia, unspecified
D46.9	Myelodysplastic syndrome, unspecified
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.C	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
D46.Z	Other myelodysplastic syndromes
D47.1	Chronic myeloproliferative disease
D47.4	Essential (hemorrhagic) thrombocythemia
D75.81	Myelofibrosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Consolidation therapy: treatment given after cancer has disappeared following initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with agents that kill cancer cells. It is also called intensification therapy and postremission therapy.

FLT3-ITD mutation – a mutation of the FMS-like tyrosine kinase 3 (FLT3) gene that includes internal tandem duplication (ITDs). ITDs of the FLT3 gene are present in approximately 30% of individuals with acute myeloid leukemia and are associated with a poor prognosis.

Myelodysplastic Syndrome (MDS): any of a group of related bone marrow disorders of varying duration preceding the development of overt acute myelogenous leukemia; they are characterized by abnormal hematopoietic stem cells, anemia, neutropenia and thrombocytopenia. Also called releukemia.

Sideroblasts: a normoblast that contains granules of iron in the form of ferritin in its cytoplasm and stains with Prussian blue. A ringed sideroblast is an abnormal sideroblast containing many iron granules in its mitochondria in a ring shape around the periphery of the nucleus.

Induction Therapy: initial treatment used to reduce cancer. Induction therapy is followed by other treatments, such as chemotherapy, radiation therapy, and hormone therapy to eliminate the cancer that remains. Also called first-line therapy, primary therapy, and primary treatment.

International Prognostic Scoring System (IPSS): classification system used in staging individuals with MDS. The IPSS evaluates three components when determining an overall score of 0 to 2.5: percent marrow blasts, cytogenics (e.g., del(5)q chromosome), and cytopenias. An IPSS score of 0 corresponds to low risk, 0.5-1 to intermediate risk 1, 1.5-2 to intermediate risk 2, and 2.5 or greater to high risk.

IPSS Classification System	
Risk Level	**IPSS Score**
Low risk	0
Intermediate risk 1	0.5-1
Intermediate risk 2	1.5-2
High risk	2.5 or greater

The following factors are used to calculate the IPSS score

	0	0.5	1.0	1.5	2.0
% Marrow Blasts	Less than 5	5-10		11-20	21-30
Cytogenetics	Normal, -Y, del(5)g alone, del(20)q alone	Other	-7, del (7)q, 3 or more abnormalities		
Cytopenias • Hemoglobin <10 g/dL Neutrophil count less than 1800/mcL • Platelet count less than 100,000 cells/mm3	Only 1	Two of the three			
ANC, absolute neutrophil count					

Revised International Prognostic Scoring System (IPSS-R): classification system used in staging individuals with MDS. Individuals are assigned to 1 of 5 risk groups.

IPSS-R Classification System	
Risk Level	**IPSS-R Score**
Very Low	≤1.5
Low	>1.5- ≤3
Intermediate	>3 - ≤4.5
High	>4.5 - ≤6
Very High	>6

The following factors are used to calculate the IPSS-R score

Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor

% Marrow Blasts	≤2	-	>2 - <5	-	5-10	>10	-
Hemoglobin	≥10	-	8 - <10	< 8	-	-	-
Platelets	≥100	50 - <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-
ANC, absolute neutrophil count							

World Health Organization (WHO) Prognostic Scoring System (WPSS): classification system used in staging individuals with MDS. This system is based on the WHO classification of the MDS subtype, karyotype, and presence of severe anemia. Individuals are assigned to 1 of 5 risk groups and the risk category may change over the course of the disease.

WPSS Classification System				
	Score			
Variable	0	1	2	3
WHO Category	RCUD, RARS, MDS with isolated del (5q)	RCMD	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	--
Severe anemia (hemoglobin <9 g/dL in males or <8 g/dL in females)	Absent	Present	--	--
RCUD, refractory cytopenia with unilineage dysplasia (includes refractory anemia, refractory neutropenia, and refractory thrombocytopenia); RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; A score of 0=very low risk, 1= low risk, 2=intermediate risk, 3-4=high risk, 5-6=very high risk				

RELATED GUIDELINES:

Oprelvekin; Interleukin 11 (Neumega®), 09-J0000-63

Lenalidomide (Revlimid®), 09-J0000-80

Carboplatin (Paraplatin®) IV, 09-J0000-93

Docetaxel (Taxotere®) IV, 09-J0000-95

Romiplostim Injection (Nplate™), 09-J0000-98

OTHER:

None applicable.

REFERENCES:

1. AHFS Drug Information. Bethesda (MD): American Society of Health-System Pharmacists, Inc; 2018 [cited 2018 Dec 21]. In: STAT!Ref Online Electronic Medical Library [Internet]. Available from: http://online.statref.com/.
2. Celgene. Vidaza (azacitidine) injection, August 2020 [cited 2020 Nov 25]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine.
3. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2021 [cited 2021 Nov 25]. Available from: http://www.clinicalpharmacology.com/.
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 2017 Nov 20]. Available from: http://clinicaltrials.gov/.

5. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2021 Nov 25].
6. National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Acute Myeloid Leukemia, v. 3.2021 [cited 2021 Nov 25]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
7. National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Myelodysplastic Syndromes, v. 2.2022 [cited 2021 Nov 25]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
8. National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Myeloproliferative Neoplasms, v. 2.2021 [cited 2021 Nov 25]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
9. NCCN Drugs & Biologics Compendium [Internet]. Fort Washington (PA): National Comprehensive Cancer Network; 2021 [cited 2021 Nov 25]. Available from: http://www.nccn.org/professionals/drug_compendium/content/contents.asp/.
10. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2020 [cited 2020 Nov 25]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Coverage Committee on 12/08/21.

GUIDELINE UPDATE INFORMATION:

01/01/09	New Medical Coverage Guideline.
01/15/10	Review and revision to guideline; consisting of adding acute myeloid leukemia as a covered indication.
01/15/11	Review and revision to guideline; consisting of updating coding, related guidelines and references.
08/17/11	Revision; ICD-10 codes updated.
01/15/12	Review and revision to guideline; consisting of revising position statement, precautions, codes and references.
01/15/13	Review and revision to guideline; consisting of revising and reformatting position statement and adding AML as covered indication; reformatting/revising description, dosage/administration, precaution sections; updating references and coding; added definitions.
01/15/14	Review and revision to guideline; consisting of updating position statement, coding, references, and program exceptions.
01/15/15	Review and revision to guideline; consisting of position statement, dosage/administration; precautions/warnings, coding, references.
10/01/15	Revision to guideline consisting of coding updates and update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
1/15/16	Review and revision to guideline; consisting of updating position statement, coding, definitions, references.
01/15/17	Review and revision to guideline; consisting of updating position statement, description, coding, precautions, and references.
01/15/18	Review and revision to guideline; consisting of updating position statement and references.
02/15/19	Review and revision to guideline; consisting of updating position statement and references.

02/15/20	Review and revision to guideline; consisting of updating position statement,coding and references.
01/15/21	Review and revision to guideline; consisting of updating the position statement and references.
01/15/22	Review and revision to guideline; consisting of updating the references.
06/01/26	Revision: Added Drug Waste Reduction statement to the Position Statement.