RXADVANCE
2 Park Central Drive
Southborough, MA 01772

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| **Clinical Policy Title:** | azacitidine |
| **Policy Number:** | RxA.549 |
| **Drug(s) Applied:** | Vidaza® |
| **Original Policy Date:** | 03/06/2020 |
| **Last Review Date:** | 12/07/2020 |
| **Line of Business Policy Applies to:** | All lines of business |

## Background

Azacitidine (Vidaza®) is a pyrimidine nucleoside analog of cytidine.

It is indicated for the treatment of 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).

## Dosing Information

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| azacitidine (Vidaza®) | MDS | 75 mg/m$^2$ SC or IV infusion once daily 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 |

## Dosage Forms

- Lyophilized powder in single dose vials: 100 mg

## Clinical Policy

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

This clinical policy has been developed to authorize, modify, or determine coverage for individuals with similar conditions. Specific care and treatment may vary depending on individual need and benefits covered by the plan. This policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. This document may contain prescription brand name drugs that are trademarks of pharmaceutical manufacturers that are not affiliated with RxAdvance.

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**I. Initial Approval Criteria**

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

1. Diagnosis of MDS;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a, b, c, d, or e):
   a. With del(5q) cytogenetic abnormality: Failure of Revlimid® at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
      *Prior *authorization may be required for Revlimid*
   b. Without del(5q) cytogenetic abnormality and serum erythropoietin ≤ 500 mU/mL: Failure of Revlimid® and one of the following agents, unless all are contraindicated or clinically significant adverse effects are experienced: epoetin alfa (e.g., Epogen®, Procrit®, Retacrit™), Aranesp®;
      *Prior authorization may be required for Revlimid, epoetin alfa, and Aranesp
   c. Without del(5q) cytogenetic abnormality and serum erythropoietin > 500 mU/mL;
   d. Has previously received stem cell transplantation, will be receiving azacitidine as a bridge while awaiting stem cell transplant donor availability, or is not a candidate for stem cell transplant;
   e. Clinically relevant (e.g., clinically severe) thrombocytopenia or neutropenia, or increased bone marrow blasts (*see Appendix D*);
5. Request meets one of the following (a, b, or c):*
   a. Initial: Dose does not exceed 75 mg/m$^2$ per day for 7 days;
   b. Maintenance: 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**
**Commercial:** 6 months
**Medicaid:** 6 months

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

1. Diagnosis of acute myeloid leukemia (AML);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed for one of the following (a, b, or c):
   a. In members age ≥ 60 years for one of the following (i, ii, or iii):
      i. As a single agent;
      ii. In combination with Nexavar® for FLT3-ITD mutation-positive disease;
         **Prior authorization may be required for Nexavar*
      iii. In combination with Venclexta®;
         **Prior authorization may be required for Venclexta*
   b. Relapsed/refractory disease for one of the following (i, ii, or iii):
      i. As a component of repeating the initial successful induction regimen if late relapse (≥ 12 months);
      ii. As a single agent;
      iii. In combination with Nexavar® for FLT3-ITD mutation-positive disease;
         **Prior authorization may be required for Nexavar*
   c. Treatment of myelofibrosis (MF)-accelerated phase or MF-blast phase/acute myeloid leukemia;
5. 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;

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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**
**Commercial:** 6 months
**Medicaid:** 6 months

**II. Continued Therapy Approval**

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

1. Member is currently receiving medication that has been authorized by RxAdvance or member has met initial approval criteria for the covered indications and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 100 mg/m$^2$ per day for 7 days per 4-week cycle;
   b. 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**
**Commercial:** 12 months
**Medicaid:** 12 months

**III. Appendices**

**APPENDIX A: Abbreviation/Acronym Key**
AML: acute myelogenous leukemia
CMMoL: chronic myelomonocytic leukemia
FAB: French-American-British
FDA: Food and Drug Administration
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

**APPENDIX B: Therapeutic Alternatives**
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| Procrit®, Epogen®, Retacrit® (epoetin alfa)* | 150 to 300 units/kg/day SC or 450 to 1,000 units/kg/day SC in divided doses 3 to 7 times per week or 60,000 units every week | Target hemoglobin up to 12 g/dL |

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| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| Aranesp® (darbepoetin alfa)* | 150 to 300 mcg SC every week or 500 mcg SC every 2 to 3 weeks | Target hemoglobin up to 12 g/dL |
| Revlimid® (lenalidomide) | 10 mg PO once daily; dosing is modified based upon clinical and laboratory findings | 25 mg/day |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

**APPENDIX C: Contraindications/Boxed Warnings**

- Contraindication(s):
  - Advanced malignant hepatic tumors;
  - Hypersensitivity to azacitidine or mannitol.

- Boxed warning(s):
  - None reported

**APPENDIX D: General Information**

- The National Comprehensive Cancer Network (NCCN) guideline for MDS recommends the use of Vidaza® or Dacogen® for initial active therapy for all subtypes of MDS with the exception of patients with 5q cytogenetic abnormality or patients with serum erythropoetin levels not more than 500 mU/mL; these patients should be treated with Revlimid and/or an erythropoietic agent such as Procrit.
- Vidaza® use for AML in elderly patients (≥ 60 years old) who are not considered eligible to receive conventional induction therapy or decline intensive therapy has an American Hospital Formulary Service (AHFS) Grade of Recommendation of reasonable (accepted), an NCCN Category rating of 2A, and is listed as an off-label indication in Clinical Pharmacology.
- Vidaza® use for relapsed or refractory AML in patients who cannot tolerate more aggressive regimens has an NCCN Category rating of 2A and is listed as an off-label indication in Clinical Pharmacology.
- RAEB-T has been reclassified as AML with multilineage dysplasia in World Health Organization (WHO) system.
- Per the revised International Prognostic Scoring System (IPSS) for MDS, clinically significant cytopenias and blast count in the setting of MDS (i.e., those which worsen the prognostic score of MDS) are:
  - Platelets < 100,000;
  - Absolute neutrophil count < 800;
  - Blast count > 2%.

**References**

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8. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndrome. Blood. 2012; 120: 2454-2465. Accessed September 18, 2020.

| Review/Revision History | Review/Revision Date | P&T Approval Date |
|---|---|---|
| Policy established. | 01/2020 | 03/06/2020 |
| Policy was reviewed<br>1. Clinical Policy title was updated to “azacitidine”.<br>2. Line of business policy applies to was updated to “All lines of business”.<br>3. HIM approval duration removed & updated.<br>4. Continued Therapy criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...".<br>5. References were reviewed and updated. | 09/18/2020 | 12/07/2020 |

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