I. PURPOSE
To define and describe the accepted indications for hypomethylating agents – Vidaza, Dacogen (azacitidine, decitabine) usage in the treatment of cancer.

II. DEFINITIONS
In some cancer cells, hypermethylation blocks the activity of tumor suppressor genes. Tumor suppressor genes regulate cell division and differentiation to prevent malignant transformation. When tumor suppressor gene activity is blocked, cell division becomes unregulated, leading to the formation of neoplastic cells.

**Hypomethylating agents:** such as Vidaza (azacitidine) and Dacogen (decitabine) regulate DNA methylation and specifically targets methyltransferase. These agents effectively demethylate and, therefore, reactivate different tumor suppressor genes which help to restore cell differentiation and/or apoptosis.

Vidaza (azacitidine) and Dacogen (decitabine) are both FDA approved for the treatment of members with myelodysplastic syndrome.

Non-FDA approved indication includes acute myeloid leukemia.

Vidaza (azacitidine) is available as 100 mg vials.
Dacogen (decitabine) is available as 50 mg vials.

III. POLICY
New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must be supported by, at minimum, two peer reviewed citations. If references are not produced, delays may occur to the processing of such request.

**Inclusion Criteria:** Vidaza (azacitidine) and Dacogen (decitabine) may be considered medically necessary when any of the following selection criteria is met:

1. **Myelodysplastic Syndrome (MDS)**
   a. The member has ONE of the following myelodysplastic syndrome subtypes:
      i. Refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS): if accompanied by neutropenia OR thrombocytopenia OR requiring transfusions
      ii. Refractory anemia with excess blasts (RAEB)
      iii. Refractory anemia with excess blasts in transformation (RAEB-T)
      iv. Chronic myelomonocytic leukemia (CMML) AND
   b. Vidaza (azacitidine) or Dacogen (decitabine) is being used with ONE of the following (refer to Attachment A for IPSS scoring):
      i. (IPSS Low and INT-1) Low risk MDS with no del(5q)
1. As initial treatment with a serum erythropoietin level > 500 mU/mL and a low probability of response to immunosuppressive therapy OR
2. As second line treatment for member who failed erythropoietin or immunosuppressive therapy OR
3. As initial treatment for thrombocytopenia, neutropenia, or increased marrow blasts.
   ii. (IPSS Low and INT-1) Low risk MDS with del(5q) AND has failed lenalidomide.
   iii. (IPSS High and INT-2) High risk MDS and ONE of the following:
       1. Not a candidate for high-intensity therapy OR
       2. Candidate for high-intensity therapy awaiting allogeneic hemopoietic stem cell transplant OR
       3. Member who has relapse after allogeneic hemopoietic stem cell transplant.

2. **Acute Myeloid leukemia (AML)**
   a. Vidaza (azacitidine) or Dacogen (decitabine) is being use for AML as a single agent for induction, postremission consolidation, OR salvage therapy AND the member is:
      i. Not eligible for intensive chemotherapy OR
      ii. Have disease that is refractory to intensive chemotherapy OR
      iii. Is ≥ 60 years old.
   b. Therapy for relapse or refractory disease in patients who cannot tolerate more aggressive regimens as a single agent or in combination with sorafenib (for FLT3-ITD mutation positive patients)

**Exclusion Criteria:** Vidaza (azacitidine) and Dacogen (decitabine) is not considered medically necessary when any of the following selection criteria is met:
1. Vidaza (azacitidine) or Dacogen (decitabine) is being used for RA or RARS not accompanied by neutropenia, thrombocytopenia, clinical hemorrhage requiring platelet transfusions, OR anemia requiring red blood cell transfusions.
2. Member with relapse disease following initial response to Vidaza (azacitidine) or Dacogen (decitabine).
3. Dosing exceeds single dose limit of Vidaza (azacitidine) of 100 mg/m².
4. Dosing exceeds single dose limit of Dacogen (decitabine) 20 mg/m².
5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

### IV. PROCEDURE

Requests for Vidaza (azacitidine) and Dacogen (decitabine) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration**
   a. MDS:
      i. Vidaza (azacitidine): 75 mg/m² SQ or IV daily for 7 days; repeat cycle every 4 weeks for as long as member benefits (minimum 4 to 6 cycles); may increase dose to 100 mg/m² if no improvement seen after 2 cycles and the only toxicity is nausea and vomiting; partial response may require additional cycles
      ii. Dacogen (decitabine):
         1. (3-day regimen) 15 mg/m² IV over 3 hr every 8 hr for 3 days repeated every 6 wk for a minimum of 4 cycles; premedicate with standard antiemetics.
         2. (5-day regimen) 20 mg/m²/day IV over 1 hr for 5 days repeated every 4 wk for a minimum of 4 cycles; premedicate with standard antiemetics.

2. **Dosage Adjustments for Vidaza (azacitidine):**
a. Hematologic:
   i. If nadir ANC < 0.5 x 10^9/L and platelets < 0.25 x 10^9/L use 50% of dose in next course; if nadir ANC is between 0.5 to 1.5 and platelets are between 25 to 50 use 67% of dose in next course; if ANC > 1.5 and platelets > 50 no dose adjustment is necessary.
   ii. If percentage of mature granulocytes and ANC is higher than at onset of the current course continue with 100% of the dose; if the % decrease in WBC or platelet nadir from baseline is between 50%-75% AND the bone marrow biopsy cellularity at nadir is between 30%-60% use 100% of the dose in the next course, if the bone marrow biopsy cellularity is less than 15% use 33% of the dose; if the % decrease in WBC or platelet nadir > 75% AND the bone marrow biopsy cellularity is 30%-60% use 75% of the dose in the next course, if the bone marrow biopsy cellularity is 15%-30% use 50% of the dose, if the bone marrow biopsy cellularity < 15% use 33% of the dose; if this occurs and both WBC and platelets > 25% above the nadir and rising, give the next course 28 days after the start of the previous course, if not then reassess counts every 7 days, if by day 42 a 25% increase is not seen then treat with 50% of the scheduled dose.

b. Bicarbonate level: if serum bicarbonate decreases to less than 20 mEq/L for unknown reasons, decrease dose by 50% on the next course.

c. Renal: if unexplained elevations of BUN or serum creatinine occur, delay next cycle until values return to normal or baseline and dose should be reduced by 50% on the next course.

3. Dosage adjustments for Dacogen (decitabine):
   a. Renal impairment: if serum creatinine of 2 mg/dL or higher, do not start next treatment cycle until toxicity resolves.
   b. Hepatic impairment: if serum glutamic pyruvic transaminase or total bilirubin of 2 X ULN or higher, do not start next treatment cycle until toxicity resolves.
   c. Hematologic toxicity (3-day regimen): for absolute neutrophil count (ANC) (at least 1000/mcL) and platelet count (at least 50,000/mcL) recovery longer than 6 wk but less than 8 wk after a treatment cycle, delay decitabine for up to 2 more wk then temporarily reduce the dose to 11 mg/m^2 IV every 8 hr for 3 days; for ANC and platelet count recovery longer than 8 wk but less than 10 wk, assess member for disease progression; if no progression, delay for up to 2 wk then reduce the dose to 11 mg/m^2 IV every 8 hr for 3 days; may maintain or re-escalate dose on subsequent cycles as indicated.
   d. Hematologic toxicity (5-day regimen): do not start next treatment cycle until the absolute neutrophil count is at least 1000/mcL and the platelet count is 50,000/mcL or greater.
   e. Infection (active or uncontrolled): do not start next treatment cycle until toxicity resolves.

4. Monitoring
   a. Vidaza (azacitidine) is contraindicated in members with advanced malignant hepatic tumors. Vidaza (azacitidine) is potentially hepatotoxic in members with severe preexisting hepatic impairment; therefore, azacitidine should be used with caution in these members.
   b. If unexplained reductions in sodium bicarbonate levels to < 20 mEq/L occur, the dosage of Vidaza (azacitidine) should be reduced by 50% in the next course. If unexplained elevations of BUN or creatinine occur, the next cycle should be delayed until the values return to normal or baseline, and the dose should be reduced by 50% in the next course.
   c. Dacogen (decitabine) should not be administered to members with transaminase > 2 times the upper limit of normal or serum bilirubin > 1.5 milligrams/deciliter, or serum creatinine > 2 milligrams/deciliter.
V. APPROVAL AUTHORITY
   1. Review – UM Department
   2. Final Approval – UM Committee

VI. ATTACHMENTS
   Attachment A: IPSS scoring system

VII. REFERENCES
# Internal Prognosis Scoring System (IPSS)

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<th>Prognostic Variable</th>
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<td>Marrow blasts (%)&lt;sup&gt;λ&lt;/sup&gt;</td>
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<td>11-20</td>
<td>21-30</td>
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<tr>
<td>Karyotype&lt;sup&gt;β&lt;/sup&gt;</td>
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<td>Intermediate</td>
<td>Poor</td>
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<tr>
<td>Cytopenia&lt;sup&gt;α&lt;/sup&gt;</td>
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<td>2/3</td>
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<sup>λ</sup>Patients with 20-29% blasts may be considered as MDS or AML.

<sup>β</sup>Cytogenetics: **Good** = normal, -Y alone, del(5q) alone, del (20q) alone; **Poor** = complex (≥ 3 abnormalities) or chromosome 7 anomalies; **Intermediate** = other abnormalities.

<sup>α</sup>Cytopenias: neutrophil count<1,800/mcL, platelets <100,000/mcL, Hb <10g/dL.

<table>
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<tr>
<th>Risk Category (% IPSS pop.)</th>
<th>Overall Score</th>
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<tr>
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<tr>
<td>INT-1 (38)</td>
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<tr>
<td>INT-2 (22)</td>
<td>1.5-2.0</td>
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<tr>
<td>HIGH (7)</td>
<td>≥2.5</td>
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Adapted from NCCN Guidelines for MDS v.2.2019