



# azacitidine (Onureg®)

## EOCCO POLICY



Policy Type: PA/SP

Pharmacy Coverage Policy: EOCCO218

### Description

Azacitidine (Onureg) is an orally administered hypomethylating agent (HMA).

### Length of Authorization

- Initial: Six months
- Renewal: 12 months

### Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
azacitidine (Onureg)	Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission	200 mg tablet	14 tablets/28 days
		300 mg tablet	

### Initial Evaluation

- I. **Azacitidine (Onureg)** may be considered medically necessary when the following criteria are met:
  - A. Member is 18 years of age or older; **AND**
  - B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
  - C. Medication will be used as monotherapy; **AND**
  - D. A diagnosis of **acute myeloid leukemia (AML)** when the following are met:
    1. Provider attestation the member has intermediate or poor-risk disease; **AND**
    2. Member has achieved first complete remission (CR) after induction chemotherapy (e.g. cytarabine, idarubicin, daunorubicin, mitoxantrone); **AND**
    3. Member received at least one cycle of consolidation chemotherapy; **OR**
      - i. Provider attests that the member is not able to receive any or all of the recommended consolidation therapy; **AND**
    4. Provider attests that the member is ineligible for allogenic hematopoietic stem cell transplant (HSCT); **AND**
  - E. Treatment with IV or subcutaneous (SC) azacitidine (Vidaza) or IV decitabine (Dacogen) has been ineffective, contraindicated, or not tolerated
- II. Azacitidine (Onureg) is considered Not Medically Necessary when used for:
  - A. Treatment of Myelodysplastic syndrome (MDS)

- III. Azacitidine (Onureg) is considered investigational when used for all other conditions, including but not limited to:
- A. Acute myeloid leukemia- newly diagnosed (Induction chemotherapy)
  - B. Acute myeloid leukemia – maintenance following allogenic HSCT
  - C. Acute myeloid leukemia – relapsed after first remission
  - D. In combination with other oncolytic agents

### Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Disease response to treatment defined by stabilization or improvement of disease (e.g. maintenance of remission; lack of disease relapse or progression)

### Supporting Evidence

- I. Azacitidine (Onureg) is an orally administered HMA FDA-approved for the treatment of AML in patients aged 18 years and older. It is indicated for patients who have achieved first CR after induction chemotherapy and/or consolidation therapy.
- II. Many treatment options exist for AML. Initial and further line therapies in this setting are contingent upon patient specific characteristics, disease-risk, and cytogenetic stratification. Given the complexities surrounding diagnosis and treatment choices, azacitidine (Onureg) must be prescribed by or in consultation with an oncologist or hematologist.
- III. Currently, AML treatment is stratified by patient age, cytogenetic and molecular risk status, actionable mutations, AML disease characteristics and classification, and the patient’s ability to tolerate intensive therapy based on comorbidities and performance status. Patients with AML are encouraged to enroll in clinical trials during any phase of treatment. Initial induction therapy for AML usually involves use of antimetabolite (e.g. cytarabine) in combination with anthracycline analogs (e.g. daunorubicin), also known as 7+3 regimen. Although majority of patients achieve CR, or complete remission with incomplete blood count recovery (CRi), post induction therapy, consolidation chemotherapy is recommended in order to prolong remission.
- IV. Historically, induction therapy utilizing an intensive chemotherapy regimen (e.g., cytarabine and an anthracycline) has been the standard of care in AML patients with a good performance status who can tolerate aggressive initial treatment. Post-remission therapy, which includes consolidation, allogeneic HSCT, maintenance, and/or continued treatment, is tailored based on the patient’s overall risk of AML relapse. Relapse rates for AML can be as high as 80% depending

on patient age, cytogenetic and molecular abnormalities, and other factors. Intensive curative therapy (e.g., allogeneic HSCT) may not be a feasible option for many older patients due to comorbidities, poor performance status, and a high risk of transplant-related mortality. Additionally, some patients experience a deterioration in their condition between the start of induction and achievement of CR, others refuse HSCT, and disadvantaged populations with high levels of poverty and living in rural geographic counties have inferior access to HSCT, such that only a minority (8%) of treated patients with AML receive an allogeneic HSCT. In such cases, additional interventions to decrease the likelihood of relapse and improve survival are practical. Consolidation with successive cycles of AML-directed therapy may be recommended for patients with relatively low risk of AML relapse, while allogeneic HSCT may be offered to eligible patients with intermediate and high risk of relapse. Azacitidine (Onureg) is indicated for continued treatment for adult patients, who had CR or CRi post induction chemotherapy, with or without consolidation, and who are unable to complete intensive curative therapy. NCCN guidelines for AML has included azacitidine (Onureg) as a maintenance therapy agent. However, consolidation chemotherapy is still a preferred option for patients with favorable risk cytogenetics and those who do not have comorbidities precluding use of intensive consolidation chemotherapy.

- V. The use of azacitidine (Onureg) has not been studied in combination with other treatment regimens for AML, such as venetoclax (Venclexta) and midostaurin (Rydapt). Due to lack of safety and efficacy data with a combination regimen, these agents should not be used together. Additionally, there is no data to support efficacy of azacitidine (Onureg) in place of HSCT, which remains the curative therapeutic alternative for majority of patients.
- VI. The efficacy and safety of azacitidine (Onureg) was evaluated in a Phase 3, double-blind, randomized, placebo-controlled trial (N= 472). Patient were randomized to receive an oral 300 mg dose of treatment or matching placebo for 14 days. Overall survival (OS) was the primary endpoint and relapse-free survival (RFS) was a key secondary outcome. Median treatment duration was 12 cycles. Patients included had intermediate or poor cytogenetic risk AML, who were not candidates for HSCT and had CR or CRi post induction and/or consolidation therapy. Patients with prior history of HMA were excluded. Overall survival for azacitidine (Onureg) treatment arm was 24.7 months (95% CI; 18.7, 30.5) as compared to that of 14.8 months (95% CI; 11.7, 17.6) for placebo the arm [hazard ratio 0.69 (95% CI; 0.55, 0.86;  $p=0.0009$ ]. Additionally, median RFS was 10.2 months vs 4.8 months for treatment vs placebo [HR 0.65 (95% CI; 0.52, 0.81;  $p=0.0001$ )].
- VII. During the clinical trial, dose escalation to a 21-day regimen of azacitidine (Onureg) was allowed for patients showing 5% to 15% bone marrow (BM) blasts during treatment phase. However, increased drug exposure did not lead to additional survival benefits. Currently, there is insufficient data to support a 21 day treatment cycle with azacitidine (Onureg).
- VIII. The most common adverse events (AE) reported for azacitidine (Onureg) during clinical trial were nausea, vomiting, and diarrhea. Additionally, grade 3 to 4 hematological AEs such as neutropenia, thrombocytopenia, and febrile neutropenia were reported. Azacitidine (Onureg)

treatment led to 13% treatment discontinuation, 43% dose interruption due to AEs, and 16% dose reduction rates.

- IX. The NCCN guideline for the treatment of AML was updated in June 2022, which upgraded the recommendation to use oral azacitidine (Onureg) as a maintenance treatment for AML to a Category 1 recommendation. This recommendation is limited to patients, who are  $\geq 55$  years of age, have intermediate to poor cytogenetic risk, and have undergone a consolidation therapy, or are unable to receive any consolidation regimens. This criteria is consistent with the clinical trial design for azacitidine (Onureg) wherein majority of trial participants were  $\geq 55$  years of age. It is important to note that the efficacy and safety of azacitidine (Onureg) have not been compared with IV or subcutaneous azacitidine (Vidaza) via a head-to-head clinical trial and the current clinical data does not establish the superiority of oral azacitidine (Onureg) over IV or SC azacitidine (Vidaza). Additionally, IV and SC azacitidine formulations remain a guideline recommended alternative for patients  $\geq 55$  years (Category 2A recommendation). IV azacitidine is not contraindicated in patients  $\geq 55$  years, nor a dose adjustment is recommended based on age. Although not FDA approved, IV and SC formulations of azacitidine (Vidaza) have been utilized as maintenance therapy of AML and are expected to remain mainstay treatment alternatives. For members  $< 55$  years of age, who are medically fit, and are not candidates for HSCT, surveillance may be considered over maintenance therapy. Although NCCN guideline recommend use of oral azacitidine (Onureg) as a maintenance treatment in this population, the NCCN panel notes that the data surrounding the efficacy of azacitidine (Onureg) in this setting is limited to the older population ( $\geq 55$  years of age). Additionally, as of June 2022, use of decitabine (Dacogen) as a maintenance therapy, has been updated to a Category 2B recommendation.
- X. The majority of the safety and efficacy data for use of hypomethylating agents in the maintenance treatment of AML are rooted in the trials for the IV and SC therapies. Approval of azacitidine (Onureg) was based on the reported survival outcomes data of this oral formulation. However, there is no evidence to suggest superiority of oral azacitidine (Onureg) over IV/SC azacitidine (Vidaza) and/or IV decitabine (Dacogen). Weighing the safety, efficacy, cost, and clinical experience, IV/ SC therapies are considered standard and appropriate high-value treatment options in this space and are preferred over azacitidine (Onureg).

### Investigational or Not Medically Necessary Uses

- I. Efficacy and safety of azacitidine (Onureg) for treatment of MDS was studied in a Phase 3 trial wherein 300 mg of azacitidine (Onureg) or a matching placebo were administered once daily for 21 days per 28-day cycle in patients with RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS (AZA-MDS-003). Although azacitidine (Onureg) treatment showed higher percentage of patients reporting RBC transfusion independence versus

placebo, the study was halted due to safety concerns related to an excess of early mortality due to hematological toxicities in the treatment arm.

- II. Azacitidine (Onureg) is currently being studied in multiple clinical trials in the settings of MDS maintenance post HSCT, for maintenance therapy after HSCT in patients with AML, and for induction chemotherapy for newly diagnosed AML. However, there are no published results for these trials indicating efficacy and safety of azacitidine (Onureg) in these conditions.

### References

1. Azacitidine (Onureg) prescribing information. Summit, NJ: Celgene Corporation; September 2020.
2. Estey, E H. Acute myeloid leukemia: 2019 update on risk-stratification and management. *Am J Hematol.* 2018;93(10):1267-1291.
3. Narayanan D, Weinberg OK. How I investigate acute myeloid leukemia. *Int J Lab Hematol.* 2020; 42:3-15.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020; 70:7-30.
5. Garcia-Manero G, Savona MR, Gore SD, et al. CC-486 (oral azacitidine) in patients with hematological malignancies who had received prior treatment with injectable hypomethylating agents (HMAs): Results from phase 1/2 CC-486 studies. *Blood (ASH Annual Meeting Abstracts)* 2016b;128: Abstract 905.

### Related Policies

Currently there are no related policies.

### Policy Implementation/Update:

Action and Summary of Changes	Date
NCCN updated recommendation (Category 1) reviewed; PA policy unchanged; updated formatting and supporting evidence	11/2022
Policy created	02/2021