BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ONUREG® (azacitidine)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Onureg (azacitidine) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Continued treatment of acute myeloid leukemia (AML) who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

b. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
   a. Negative pregnancy test in a woman of childbearing potential
   b. Eastern Cooperative Oncology Group (ECOG) Performance Status score is 0-2

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Will not be a substitute for intravenous or subcutaneous azacitidine

7. Will not be used to treat myelodysplastic syndromes (MDS)

8. Will not be used in moderate or severe hepatic impairment (total bilirubin greater than 1.5 times the upper limit of normal)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Onureg (azacitidine) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual has documentation of positive clinical response to therapy defined as the following:
   a. No evidence of disease progression
   b. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Myelosuppression that recurs in two consecutive cycles despite treatment interruption, dose reduction, reduced treatment duration, and schedule reduction
   b. Gastrointestinal toxicity (nausea, vomiting, or diarrhea) that recurs despite treatment interruptions, dose reduction, reduced treatment duration, and schedule reduction
   c. Other adverse reaction that recurs despite treatment interruptions, dose reduction, reduced treatment duration, and schedule reduction

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

d. Interstitial lung disease
e. Tumor lysis syndrome
f. Sweet's syndrome (acute febrile neutrophilic dermatosis)
g. Necrotizing fasciitis
h. Differentiation syndrome

6. Will not be a substitute for intravenous or subcutaneous azacitidine

7. Will not be used to treat myelodysplastic syndromes (MDS)

8. Will not be used in moderate or severe hepatic impairment (total bilirubin greater than 1.5 times the upper limit of normal)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Onureg (azacitidine) is a nucleoside metabolic inhibitor indicated for continued treatment of adult patients with acute myeloid leukemia (AML) who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

Azacitidine is a pyrimidine nucleoside analog of cytidine that inhibits DNA/RNA methyltransferases. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates.

Treatment of AML is determined by the ability or fitness of the individual for intensive anti-leukemic therapy based upon the patient's performance status and physiologic function from comorbid conditions. For most medically-fit patients who undergo intensive induction therapy for AML, the goal of treatment is to achieve long-term-survival with the possibility of cure. Medically-unfit but not frail patients that are unlikely to tolerate intensive anti-leukemic therapy, the goal of treatment is to achieve a remission, improve quality of life, and/or prolong life. Frail AML patients are those patients whose debility or comorbid conditions do not permit treatments that modify the disease course as the potential for harms from intensive therapy outweighs the benefits. The goals of managing these patients is to relive symptoms and improve quality of life through supportive care measures.

Medically-unfit but not frail patients are not candidates for intensive anti-leukemic therapy. Hypomethylating agents (HMA) such as azacitidine or decitabine are the mainstays of treatment; usually combined with the B-cell lymphoma-2 (BCL2) inhibitor venetoclax rather than use of HMA or BCL2 agents as monotherapy. For patients

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

with an actionable mutation such as an isocitrate dehydrogenase (IDH 1 or IDH2) mutation, use of an IDH inhibitor (ivosidenib for IDH1 mutation or enasidenib for IDH2 mutation) is an alternative to HMA-based therapy. Low dose cytarabine (LoDAC) can be used when the patient is not eligible for an HMA and who does not have an actionable mutation or an available target agent.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Response definitions:
Based on blood counts, transfusion needs, and relief of symptoms

- **Complete response (CR)**
  - Normalization of the complete blood count (CBC), including absolute neutrophil count (ANC) ≥1000/microL and platelets ≥100,000/microL, transfusion-independence, and relief of AML-related symptoms
- **CR with incomplete hematologic recovery (CRi)**
  - Transfusion-independent and meets above criteria for CR, but without complete platelet recovery (usually) or ANC recovery
- **Partial response (PR)**
  - Improvements in CBC, but not to levels that define CR/Cri with ongoing transfusion needs and/or inadequate symptom relief
- **Refractory disease**
  - No meaningful improvement in CBC, ongoing transfusion needs, and/or inadequate symptom relief

---

Resources:

Onureg (azacitidine) oral product information, revised by Celgene Corporation 10-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 24, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Myeloid Leukemia Version 2.2026 – Updated October 02, 2025. Available at https://www.nccn.org. Accessed October 09, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.