BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

IDHIFA® (enasidenib) oral
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:** Idhifa (enasidenib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** 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. Relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test

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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 received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Negative pregnancy test in a woman of child-bearing potential
   b. Eastern Cooperative Oncology Group (ECOG) Performance Status 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)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Idhifa (enasidenib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** 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's condition has responded while on therapy with response defined as there is no evidence of disease progression or unacceptable toxicity

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 other significant adverse drug effects that recurs after dose adjustment that may exclude continued use such as:
   a. Differentiation syndrome with severe pulmonary symptoms and/or renal dysfunction
   b. Serious or life-threatening toxicity considered related to treatment including tumor lysis syndrome
   c. Noninfectious leukocytosis

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**

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Description:

Idhifa (enasidenib) is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test. Select patients for the treatment of AML with Idhifa (enasidenib) based on the presence of IDH2 mutations in the blood or bone marrow.

Enasidenib is a small molecule inhibitor of the IDH2 enzyme. It targets the mutant IDH2 variants R140Q, R172S, and R172K. Inhibition of the mutant IDH2 enzyme leads to decreased 2-hydroxyglutarate (2-HG) levels, reduces blast counts and increases the percentage of mature myeloid cells.

Isocitrate dehydrogenase (IDH) is a key metabolic enzyme for cellular respiration in the tricarboxylic acid (TCA) cycle. There are three subtypes of IDH: IDH1, IDH2, and IDH3. IDH2 and IDH3 are found in mitochondria while IDH1 is located in the cytoplasm and peroxisomes. IDH1 and IDH2 convert isocitrate to alpha-ketoglutarate. Recurrent mutations in *IDH1* or *IDH2* genes are prevalent in several cancers including glioma, acute myeloid leukemia (AML), intrahepatic cholangiocarcinoma, and chondrosarcoma. IDH2 mutations have been reported in 8-12% of patients with AML.

In AML, complete response or remission (CR) is defined as a patient who is independent of transfusions (absolute neutrophil count > 1,000/mcL, platelets $\geq$ 100,000 mcL), normal cytogenetics (if previously abnormal), and negative molecular studies. Partial remission (PR) is defined as a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and normalization of blood counts.

Relapse following CR is defined as reappearance of leukemic blasts in the blood or more than 5% in the bone marrow that is not attributed to another cause or extramedullary relapse. Refractory or resistant disease (RD) is failure to achieve CR or achieve a complete remission with incomplete recovery (CRi).

Treatment of AML is usually through induction chemotherapy and post-remission (consolidation) therapy. It is important that a patient emerge from induction therapy in a condition that can tolerate consolidation therapy. Regimens are selected on the basis of age of the patient, patient performance status, functional status, co-morbidities, intensity for response (aggressive/intensive or less aggressive/less intensive), cytogenetic markers, and molecular markers. Patients that do not receive post-remission therapy may experience relapse. Therapy for relapsed or refractory disease may include aggressive therapy for appropriate patients, less aggressive therapy, therapy directed towards patients who have molecular abnormalities, such as FLT3-ITD disease, or other targeted therapies based on molecular mutations, such as IDH.

Aggressive therapy in an appropriate patient may include various combinations of cladribine, cytarabine, mitoxantrone, idarubicin, fludarabine, etoposide, or clofarabine. Less aggressive or less intensive treatment may include combinations of azacytidine, decitabine, venetoclax or low dose cytarabine. Sorafenib may be used in combination with azacytidine or decitabine for individuals with FLT3-ITD disease.

Definitions:

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

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ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Relapse is reappearance of leukemic blasts in the blood or ≥ 5% in the bone marrow that is not attributed to another cause or extramedullary relapse

Refractory or resistant disease is failure to achieve a complete remission or achieve a complete remission with incomplete recovery

Resources:

Idhifa (enasidenib) product information, revised by Celgene Corporation 12-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 24, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Myeloid Leukemia Version 3.2024. Updated May 17, 2024. Available at https://www.nccn.org. Accessed June 24, 2024.

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.

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