BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES		**ORIGINAL EFFECTIVE DATE:**	**9/21/2017**
SECTION:	**DRUGS**	**LAST REVIEW DATE:**	**8/19/2021**
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IDHIFA® (enasidenib) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

IDHIFA® (enasidenib) oral

Criteria:

- **Criteria for initial therapy:** Idhifa (enasidenib) 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. A confirmed diagnosis of **ONE** of the following:
     a. Relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation positive for IDH2 variants R140Q, R172S, and R172K as detected in blood or bone marrow

     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. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring 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. There are no significant interacting drugs

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Idhifa (enasidenib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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

  2. Individual's condition responded while on therapy
     a. Response is defined as
        i. No evidence of disease progression
        ii. Documented evidence of efficacy, disease stability and/or improvement

  3. Individual has been adherent with the medication

  4. Individual has not developed any significant adverse drug effects that may exclude continued use
     a. Significant adverse effect such as:
        i. Differentiation syndrome
        ii. Tumor lysis syndrome
        iii. Noninfectious leukocytosis

5. There are no significant interacting drugs

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 a Non-cancer Medications**
2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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.

IDHIFA® (enasidenib) oral

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 therapy may include 5-azacytidine, decitabine, or low dose cytarabine. Sorafenib may be used in combination with 5-azacytidine or decitabine for individuals with FLT3-ITD disease.

Definitions:

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 11-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on June 23, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Myeloid Leukemia Version 3.2021 – Updated March 02, 2021. Available at https://www.nccn.org. Accessed on June 23, 2021.

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.