BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 9/21/17**
SECTION: DRUGS	**LAST REVIEW DATE: 9/20/18**
	LAST CRITERIA REVISION DATE: 9/20/18
	ARCHIVE DATE:

IDHIFA® (enasidenib) oral tablet

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.**

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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 an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - 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
     - 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, 2A, or 2B

  4. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - A woman of child bearing potential must have a negative pregnancy test before starting treatment
     - Complete blood count with differential
     - Comprehensive metabolic panel

  5. Woman patient of child bearing potential should use effective contraception during and for at least 1 month after therapy

  6. Woman patient who is breast feeding an infant or child should stop breast feeding during and for at least 1 month after therapy

  7. Male patient with a female partner of reproductive potential should use effective contraception during and for at least 1 month after therapy

  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. Continues to be seen by an Oncologist

  2. The condition has worsened while on therapy
     - Worsening is define as lack of a complete remission or lack of complete remission with partial hematologic recovery.
       - Complete remission is defined as < 5% of blasts in the bone marrow, no evidence of disease, and full recovery of partial recovery of peripheral blood counts (platelets > 100,000/microliter and ANC > 1,000/microliter).

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- Complete remission with partial recovery is defined as < 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter)

3. Individual has been adherent with the medication

4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use, such as:
   - Differentiation syndrome
   - Tumor lysis syndrome
   - Noninfectious leukocytosis

5. There are no significant interacting drugs

Renewal duration: 12 months

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 ≥ 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).

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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 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.

NCCN Clinical Practice Guidelines in Oncology: Acute myeloid leukemia. Version 2.2018, Aug 1, 2018
Idhifa (enasidenib) Category 2A:
Used as a single agent in patients age ≥ 60 years with IDH-2 mutated AML for
- treatment induction when not a candidate for intensive remission induction therapy or declines intensive therapy
- post-remission therapy following response to previous lower intensity therapy

For relapsed/refractory disease in patients with IDH-2 mutated AML
- as a component of repeating the initial successful induction regimen if late relapse (≥12 months)
- as a single agent

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). Package Insert. Revised by manufacturer 08-2017. Accessed 09-17-2017, 07-19-2018, 08-20-18

NCCN Clinical Practice Guidelines in Oncology: Acute myeloid leukemia. Version 3.2017, June 6, 2017. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

NCCN Clinical Practice Guidelines in Oncology: Acute myeloid leukemia. Version 2.2018, Aug 1, 2018. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

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UpToDate: Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-manifestations-pathologic-features-and-diagnosis-of-acute-myeloid-leukemia?source=search_result&search=acute%20myeloid%20leukemia&selectedTitle=2~150

UpToDate: Treatment of acute myeloid leukemia in older adults. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-acute-myeloid-leukemia-in-older-adults?source=search_result&search=acute%20myeloid%20leukemia&selectedTitle=4~150#H29

UpToDate: Induction therapy for acute myeloid leukemia in younger adults. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/induction-therapy-for-acute-myeloid-leukemia-in-younger-adults?source=search_result&search=acute%20myeloid%20leukemia&selectedTitle=3~150

UpToDate: Remission criteria in acute myeloid leukemia and monitoring for residual disease. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/remission-criteria-in-acute-myeloid-leukemia-and-monitoring-for-residual-disease?source=search_result&search=Remission%20criteria%20in%20acute%20myeloid%20leukemia%20and%20monitoring%20for%20residual%20disease&selectedTitle=1~150

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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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.