Clinical Policy: Enasidenib (Idhifa)

Reference Number: CP.PHAR.363
Effective Date: 09.05.17
Last Review Date: 11.26
Line of Business: Commercial, HIM/ICHRA, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Enasidenib (Idhifa®) is an isocitrate dehydrogenase-2 (IDH2) inhibitor.

FDA Approved Indication(s)

Idhifa is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation as detected by an FDA-approved test.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Idhifa is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Acute Myeloid Leukemia (must meet all)**:**

1. Diagnosis of AML;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Idhifa is prescribed for induction, post-induction, or consolidation therapy and both of the following (i and ii):
      i. Idhifa is prescribed as single-agent therapy or in combination with azacitidine;
      ii. Member was not a suitable candidate for or declined intensive induction chemotherapy;
   b. Both of the following (i and ii):
      i. Disease is relapsed or refractory;
      ii. Idhifa is prescribed as single-agent therapy;
5. Presence of an IDH2 mutation;
6. For Idhifa requests, member must use generic enasidenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed both of the following (i and ii):
      i. 100 mg per day;
      ii. 1 tablet per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration: 12 months

B. Myelodysplastic Syndromes (off-label) (must meet all)**:**
1. Diagnosis of MDS;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Disease is one of the following (a or b):
   a. Disease is lower-risk (i.e., IPSS-R [very low, low, intermediate]) and member presents with one of the following (i or ii):
      i. Clinically relevant thrombocytopenia or neutropenia;
      ii. Symptomatic anemia;
   b. Disease is higher-risk (i.e., IPSS-R [intermediate, high, or very high]);
5. Presence of an IDH2 mutation;
6. Prescribed as subsequent therapy;
7. Prescribed as a single agent;
8. For Idhifa requests, member must use generic enasidenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
9. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Idhifa for a covered indication and has received this medication for at least 30 days;

2. Member is responding positively to therapy;
3. For Idhifa requests, member must use generic enasidenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed both of the following (i and ii):
      i. 100 mg per day;
      ii. 1 tablet per day;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration: 12 months

B. Other diagnoses/indications(must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AML: acute myeloid leukemia
FDA: Food and Drug Administration
IDH2: isocitrate dehydrogenase-2
IPSS-R: revised International Prognostic Scoring System
MDS: myelodysplastic syndromes
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of MDS therapies: azacitidine, decitabine ± cedazuridine, lenalidomide, antithymocyte globulin ± cyclosporine ± eltrombopag, high-intensity chemotherapy regimens (e.g., idarubicin-, cytarabine-, fludarabine-, and topotecan-based regimens), Reblozyl® (luspatercept-aamt), Revlimid® (lenalidomide), Rytelo™ (imetelstat)	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): none reported
- Boxed warning(s): differentiation syndrome. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
AML	100 mg PO QD	100 mg/day

VI. Product Availability
Tablets: 50 mg, 100 mg

VII. References
1. Idhifa Prescribing Information. Summit, NJ: Celgene Corporation; January 2025 Available at: https://packageinserts.bms.com/pi/pi_idhifa.pdf. Accessed July 7, 2026.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 15, 2026.
3. National Comprehensive Cancer Network. Acute Myeloid Leukemia Version 5.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed August 15, 2026.
4. National Comprehensive Cancer Network. Myelodysplastic Syndromes Version 3.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed August 15, 2026.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2022 annual review: legacy WCG approval duration consolidated; in patients age ≥ 60 years, added Idhifa must be used	08.02.22	11.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
as a single agent and option to decline intensive therapy per NCCN; references reviewed and updated. Template changes applied to other diagnoses/indications.		
4Q 2023 annual review: clarified use as a single agent for all AML indications per NCCN; references reviewed and updated.	08.09.23	11.23
4Q 2024 annual review: consolidated NCCN Compendium scenarios and removed age ≥ 60 years requirement for use in non-relapsed/refractory disease per NCCN; added Idhifa combination with azacitidine per NCCN; references reviewed and updated.	07.17.24	11.24
4Q 2025 annual review: revised initial approval durations for all lines of business to 12 months; references reviewed and updated.	07.09.25	11.25
4Q 2026 annual review: for AML, added induction, post-induction, or consolidation therapy use; added monotherapy use requirement for relapsed/refractory AML per NCCN; added MDS indication criteria per NCCN; for continued therapy, revised "AML" to "a covered indication;" revised continued therapy authorization duration for Commercial line of business from "12 months or duration of request, whichever is less" to "12 months;" added ICHRA line of business; references reviewed and updated.	07.07.26	11.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to

applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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