IDHIFA® (enasidenib) is indicated for the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

FOR PATIENTS WITH R/R AML AND AN IDH2 MUTATION

TARGETED THERAPY BEGINS WITH A TEST

WARNING: DIFFERENTIATION SYNDROME

Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed WARNING.
AML IS A COMPLEX, HETEROGENEOUS DISEASE DRIVEN BY MULTIPLE GENE MUTATIONS, INCLUDING IDH2\textsuperscript{1,2}

In a recent analysis of 200 patients with de novo AML:

- More than 99% had at least 1 mutation associated with the disease, and the majority had multiple mutations\textsuperscript{3}
- 8% to 19% of patients with AML have an IDH2 mutation, which is readily detected by molecular profiling\textsuperscript{4,5}

There is an unmet need for additional treatment options in patients with R/R AML and an IDH2 mutation.

IT'S TIME FOR A TARGETED APPROACH

- **The right patient**: Undergoes molecular profiling to identify driver mutations\textsuperscript{6}
- **The right time**: When AML has relapsed or is refractory
- **The right drug**: Targets a driver mutation of AML\textsuperscript{6}
## KEY CONSIDERATIONS FOR *IDH2* TESTING IN R/R AML

<table>
<thead>
<tr>
<th>WHY</th>
<th>Despite progress in the understanding of the pathophysiology of AML, prognosis following relapse remains poor. There is a targeted therapy specifically approved for patients with an <em>IDH2</em> mutation, and <em>IDH2</em> testing can help identify candidates for this treatment.</th>
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<tbody>
<tr>
<td>WHEN</td>
<td>The 2017 CAP-ASH Guidelines recommend testing for <em>IDH2</em> mutations during diagnostic workup. Many patients will undergo molecular testing when their disease relapses or when they become refractory to a prior therapy. <em>IDH2</em> testing can be performed at diagnosis and relapse in parallel with cytogenetics.</td>
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<tr>
<td>HOW</td>
<td>Molecular profiling of <em>IDH2</em> mutations can be performed on bone marrow or peripheral blood using an FDA-approved test.</td>
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<tr>
<td>WHERE</td>
<td>Testing can be done with an FDA-approved test in an established Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. Your pathologist may be able to perform an FDA-approved test in-house to identify <em>IDH2</em> mutations.</td>
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**THE 2017 CAP-ASH GUIDELINES**

recommend testing for *IDH2* mutations during diagnostic workup.
When a patient presents with R/R AML...

**TEST**
for IDH2 mutations

**TRIGGER**
treatment decisions in patients
with an IDH2 mutation

**TREAT**
appropriate patients
with IDHIFA*

*For treatment with IDHIFA, patients’ IDH2 mutations should be detected by an FDA-approved test. In the clinical trial, patients’ IDH2 mutations were either prospectively identified or retrospectively confirmed by an FDA-approved test.

**SELECTED SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Differentiation Syndrome: See Boxed WARNING.** In the clinical trial, 14% of patients treated with IDHIFA experienced differentiation syndrome, which may be life-threatening or fatal if not treated. Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, as early as 10 days and at up to 5 months after IDHIFA initiation. Symptoms in patients treated with IDHIFA included acute respiratory distress represented by dyspnea and/or hypoxia and need for supplemental oxygen; pulmonary infiltrates and pleural effusion; renal impairment; fever; lymphadenopathy; bone pain; peripheral edema with rapid weight gain; and pericardial effusion. Hepatic, renal, and multi-organ dysfunction have also been observed.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed WARNING.
IDHIFA, THE ONLY NON-CYTOTOXIC, TARGETED INHIBITOR OF THE IDH2 ENZYME, RELEASES THE BLOCK ON MYELOID DIFFERENTIATION

NORMAL MARROW\(^{11-15}\)

\[
\text{IDH2} \rightarrow \text{ISOCITRATE} \rightarrow \text{α-KG}
\]

The normal IDH2 enzyme converts isocitrate to α-ketoglutarate (α-KG), a substrate for enzymes essential to gene expression and myeloid differentiation.

DIFFERENTIATION BLOCKED\(^{11-15}\)

\[
\text{IDH2} \rightarrow \text{ISOCITRATE} \rightarrow \text{α-KG} \rightarrow \text{2-HG}
\]

Mutated IDH2 converts α-KG to 2-hydroxyglutarate (2-HG), an oncometabolite that leads to a block on myeloid differentiation and results in myeloblast proliferation.

DIFFERENTIATION RESTORED\(^{16}\)

\[
\text{IDH2} \rightarrow \text{MUTATED IDH2} \rightarrow \text{ISOCITRATE} \rightarrow \text{α-KG} \rightarrow \text{2-HG} \rightarrow \text{IDHIFA}
\]

In preclinical studies, IDHIFA blocked the conversion of α-KG to 2-HG. In patient blood samples, IDHIFA decreased 2-HG levels and induced myeloid differentiation.

SELECTED SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT’D)

Differentiation syndrome (cont’d): If differentiation syndrome is suspected, initiate systemic corticosteroids and hemodynamic monitoring until improvement. Taper corticosteroids only after resolution of symptoms. Differentiation syndrome symptoms may recur with premature discontinuation of corticosteroids. If severe pulmonary symptoms requiring intubation or ventilator support and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids, interrupt IDHIFA until signs and symptoms are no longer severe. Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

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In this challenging clinical setting, IDHIFA OPENS UP THE EFFICACY

IDHIFA was studied in an open-label, single-arm, multicenter, clinical trial of patients with R/R AML and an IDH2 mutation who were assigned a starting dose of 100 mg daily until disease progression or unacceptable toxicity. Dose reductions were allowed to manage adverse events. Patients’ IDH2 mutations were either prospectively identified or retrospectively confirmed by the Abbott RealTime™ IDH2 assay.* Patients were a median of 68 years old and had a median of 2 prior therapies.

Efficacy was established on the basis of the rate of CR/CRh, the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence.† The median follow-up was 6.6 months (range, 0.4 to 27.7).

23% rate of complete response (CR)‡ or CR with partial hematologic recovery (CRh)§

n=46/199
(95% CI, 18%-30%)

8.2 mo median duration of CR/CRh||

n=46/199
(95% CI, 4.3-19.4)

34% rate of conversion from transfusion dependence to transfusion independence (RBC and platelet)

n=53/157

IDHIFA works differently—treat for a minimum of 6 months to allow time for clinical response in patients without disease progression or unacceptable toxicity.

- Of the 46 patients who achieved a best response of CR/CRh, 39 (85%) did so within 6 months of initiating IDHIFA

* Abbott RealTime™ IDH2 assay is the FDA-approved test for selection of patients with AML for treatment with IDHIFA.

† Patients were defined as transfusion independent if they received no RBC or platelet transfusions within any 56-day post-baseline period.

‡ CR was defined as <5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/μL and ANC >1,000/μL).

§ CRh was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/μL and ANC >500/μL).

|| Duration of CR/CRh was defined as time since first response of CR or CRh to relapse or death, whichever is earlier.

ANC, absolute neutrophil counts; CI, confidence interval.

SELECTED SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT’D)

Embryo-Fetal Toxicity: Based on animal embryo-fetal toxicity studies, IDHIFA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose. Pregnant women, patients becoming pregnant while receiving IDHIFA, or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

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SELECTED SAFETY INFORMATION
ADVERSE REACTIONS
• The most common adverse reactions (≥20%) included total bilirubin increased (81%), calcium decreased (74%), nausea (50%), diarrhea (43%), potassium decreased (41%), vomiting (34%), decreased appetite (34%), and phosphorus decreased (27%).
• The most frequently reported ≥Grade 3 adverse reactions (≥5%) included total bilirubin increased (15%), potassium decreased (15%), phosphorus decreased (8%), calcium decreased (8%), diarrhea (8%), differentiation syndrome (7%), non-infectious leukocytosis (6%), tumor lysis syndrome (6%), and nausea (5%).
• Serious adverse reactions were reported in 77.1% of patients. The most frequent serious adverse reactions (≥2%) were leukocytosis (10%), diarrhea (6%), nausea (5%), vomiting (3%), decreased appetite (3%), tumor lysis syndrome (5%), and differentiation syndrome (8%). Differentiation syndrome events characterized as serious included pyrexia, renal failure acute, hypoxia, respiratory failure, and multi-organ failure.

LACTATION
Many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with IDHIFA and for at least 1 month after the last dose.


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**IDH2 TESTING IN R/R AML AT A GLANCE**

- **TEST FOR IDH2 MUTATIONS**
  - The 2017 CAP-ASH guidelines recommend testing for IDH2 mutations during diagnostic workup. Testing for IDH2 mutations may be conducted using an FDA-approved test.

- **TRIGGER TREATMENT DECISIONS**
  - Because IDHIFA is a targeted therapy approved for patients with an IDH2 mutation, IDH2 testing can help identify candidates for IDHIFA.

- **TREAT APPROPRIATE PATIENTS WITH IDHIFA**
  - IDHIFA is the only non-cytotoxic, targeted inhibitor of the IDH2 enzyme.
  - IDHIFA releases the block on myeloid differentiation.
    - IDHIFA selectively reduced blast cell counts and increased percentages of mature and functional myeloid cells in blood samples from patients with AML and an IDH2 mutation.

Talk to your pathologist about including IDH2 in your AML profiling panel.

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