HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IDHIFA safely and effectively. See full prescribing information for IDHIFA.

IDHIFA® (enasidenib) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: DIFFERENTIATION SYNDROME

See full prescribing information for complete boxed warning.

Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution (5.1, 6.1).

----------INDICATIONS AND USAGE----------
IDHIFA is an isocitrate dehydrogenase-2 inhibitor 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 (1.1).

----------DOSAGE AND ADMINISTRATION----------
100 mg orally once daily until disease progression or unacceptable toxicity (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 50 mg or 100 mg (3).

----------CONTRAINDICATIONS----------
None (4).

----------WARNINGS AND PRECAUTIONS----------
Embryo-Fetal Toxicity: IDHIFA can cause fetal harm. Advise patients of the potential risk to a fetus and use effective contraception (5.2, 8.1, 8.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥20%) are nausea, vomiting, diarrhea, elevated bilirubin, and decreased appetite (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
OATP1B1, OATP1B3, BCRP, and P-gp Substrates: Decrease the dosage of these substrates as recommended in its prescribing information when coadministered with IDHIFA, and as clinically indicated (7.1).

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Acute Myeloid Leukemia

IDHIFA 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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of AML with IDHIFA based on the presence of IDH2 mutations in the blood or bone marrow *[see Indications and Usage (1.1) and Clinical Studies (14.1)]*. Information on FDA-approved tests for the detection of IDH2 mutations in AML is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosage of IDHIFA is 100 mg taken orally once daily with or without food until disease progression or unacceptable toxicity. For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response.

Do not split or crush IDHIFA tablets. Administer IDHIFA tablets orally about the same time each day. If a dose of IDHIFA is vomited, missed, or not taken at the usual time, administer the dose as soon as possible on the same day, and return to the normal schedule the following day.

2.3 Monitoring and Dosage Modifications for Toxicities

Assess blood counts and blood chemistries for leukocytosis and tumor lysis syndrome prior to the initiation of IDHIFA and monitor at a minimum of every 2 weeks for at least the first 3 months during treatment. Manage any abnormalities promptly *[see Adverse Reactions (6.1)]*.

Interrupt dosing or reduce dose for toxicities. See Table 1 for dosage modification guidelines.

Table 1: Dosage Modifications for IDHIFA-Related Toxicities

Adverse Reaction	Recommended Action
• Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring *[see Warnings and Precautions (5.1)]*. • Interrupt IDHIFA if severe pulmonary symptoms requiring intubation or ventilator support, and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids *[see Warnings and Precautions (5.1)]*. • Resume IDHIFA when signs and symptoms improve to Grade 2* or lower.
• Noninfectious leukocytosis (white blood cell [WBC] count greater than 30 x 10^9/L)	• Initiate treatment with hydroxyurea, as per standard institutional practices. • Interrupt IDHIFA if leukocytosis is not improved with hydroxyurea, and then resume IDHIFA at 100 mg daily when WBC is less than 30 x 10^9/L.
• Elevation of bilirubin greater than 3 times the upper limit of normal (ULN) sustained for ≥2 weeks without elevated transaminases or other hepatic disorders	• Reduce IDHIFA dose to 50 mg daily. • Resume IDHIFA at 100 mg daily if bilirubin elevation resolves to less than 2 x ULN.
• Other Grade 3* or higher toxicity considered related to treatment including tumor lysis syndrome	• Interrupt IDHIFA until toxicity resolves to Grade 2* or lower. • Resume IDHIFA at 50 mg daily; may increase to 100 mg daily if toxicities resolve to Grade 1* or lower. • If Grade 3* or higher toxicity recurs, discontinue IDHIFA.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening.

3 DOSAGE FORMS AND STRENGTHS

IDHIFA is available in the following tablet strengths:

- 50-mg tablet: Pale yellow to yellow oval-shaped film-coated tablet debossed “ENA” on one side and “50” on the other side.
- 100-mg tablet: Pale yellow to yellow capsule-shaped film-coated tablet debossed “ENA” on one side and “100” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome

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 is associated with rapid proliferation and differentiation of myeloid cells. While there is no diagnostic test for differentiation syndrome, symptoms in patients treated with IDHIFA included acute respiratory distress represented by dyspnea and/or hypoxia (68%) and need for supplemental oxygen (76%); pulmonary infiltrates (73%) and pleural effusion (45%); renal impairment (70%); fever (36%); lymphadenopathy (33%); bone pain (27%); peripheral edema with rapid weight gain (21%); and pericardial effusion (18%). Hepatic, renal, and multi-organ dysfunction have also been observed.

Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, in as early as 1 day and up to 5 months after IDHIFA initiation.

If differentiation syndrome is suspected, initiate oral or intravenous corticosteroids (e.g., dexamethasone 10 mg every 12 hours) and hemodynamic monitoring until improvement. Taper corticosteroids only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. 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 *[see Dosage and Administration (2.3)]*. Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

5.2 Embryo-Fetal Toxicity

Based on animal embryo-fetal toxicity studies, IDHIFA can cause embryo-fetal harm when administered to a pregnant woman. In animal embryo-fetal toxicity studies, enasidenib caused embryo-fetal toxicities starting at 0.1 times the steady state clinical exposure based on the area under the concentration-time curve (AUC) at the recommended human dose.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 2 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 2 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Differentiation Syndrome *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of single-agent IDHIFA is based on 214 patients with relapsed or refractory AML who were assigned to receive 100 mg daily *[see Clinical Studies (14.1)]*. The median duration of exposure to IDHIFA was 4.3 months (range 0.3 to 23.6). The 30-day and 60-day mortality rates observed with IDHIFA were 4.2% (9/214) and 11.7% (25/214), respectively.

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.

Overall, 92 of 214 patients (43%) required a dose interruption due to an adverse reaction; the most frequent adverse reactions leading to dose interruption were differentiation syndrome (4%) and leukocytosis (3%). Ten of 214 patients (5%) required a dose reduction due to an adverse reaction; no adverse reaction required dose reduction in more than 2 patients. Thirty-six of 214 patients (17%) permanently discontinued IDHIFA due to an adverse reaction; the most frequent adverse reaction leading to permanent discontinuation was leukocytosis (1%).

The most common adverse reactions (≥20%) of any grade were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite.

Adverse reactions reported in the trial are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥10% (Any Grade) or ≥3% (Grade 3-5) of Patients with Relapsed or Refractory AML

	IDHIFA (100 mg daily) N=214	
Body System Adverse Reaction	**All Grades N=214 n (%)**	**≥Grade 3 N=214 n (%)**
Gastrointestinal Disorders [a]		
Nausea	107 (50)	11 (5)
Diarrhea	91 (43)	17 (8)
Vomiting	73 (34)	4 (2)
Metabolism and Nutrition Disorders		
Decreased appetite	73 (34)	9 (4)
Tumor lysis syndrome [b]	13 (6)	12 (6)
Blood and Lymphatic System Disorders		
Differentiation syndrome [c]	29 (14)	15 (7)
Noninfectious leukocytosis	26 (12)	12 (6)

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