Drug Monograph

A - Drug Name

enasidenib

COMMON TRADE NAME(S): Idhifa®

Enasidenib has been withdrawn from the Canadian market as of June 30th, 2023.

Enasidenib failed to demonstrate improved overall survival when compared to conventional care regimens in a Phase 3 confirmatory study. The safety profile remains unchanged.

Healthcare professionals are advised to:

- NOT initiate enasidenib in new patients;
- discuss with their patients whether to continue treatment with enasidenib;
- apply to Health Canada's Special Access Program (SAP) to request enasidenib for patients who require continued treatment.

Refer to the Health Canada communication for details.

back to top

B - Mechanism of Action and Pharmacokinetics

Enasidenib inhibits the mutant isocitrate dehydrogenase 2 (IDH2) enzyme. Mutant IDH2 enzyme catalyzes the production of the oncogenic metabolite 2-hydroxyglutarate (2-HG), which blocks cell differentiation. Inhibition of IDH2 enzyme leads to reduced 2-HG levels, induced myeloid differentiation, decreased myeloblasts counts and increased percentage of mature myeloid cells.

Absorption	Bioavailability	57%
	Effects with food	Consumption of a high fat, high calorie meal increased AUC by 50% and Cmax by 63%. Food does not appear to have any

		clinically important effects.
	Peak plasma levels	4 h (single dose); 2.15 h (steady-state)
	Time to reach steady state	29 days
Distribution	PPB	98.5% (parent) and 96.6% (active metabolite) to human plasma protein
Metabolism	Metabolized by multiple CYP enzymes and multiple UGTs.	
	Active metabolites	Yes
Elimination	Enasidenib is primarily excreted in feces.	
	Feces	89% (34% unchanged)
	Urine	11% (0.4% unchanged)
	Half-life	terminal: 7.9 days

back to top

C - Indications and Status

Enasidenib has been withdrawn from the Canadian market as of June 30th, 2023.

Previous Indication:

For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation

back to top

D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

The following adverse effects include those reported in ≥ 10% of patients with relapsed or refractory AML in a Phase I/II study. Severe or life-threatening adverse events may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Heart failure (<10%)	D
Gastrointestinal	Anorexia (19%)	E D
	Diarrhea (15%)	E
	Nausea, vomiting (28%)	E
General	Fatigue (15%)	E D
	Other (13%) (differentiation syndrome, 7% severe)	E D
Hematological	Disseminated intravascular coagulation (<10%)	E
	Leukocytosis (8%) (2% severe)	E D
	Myelosuppression ± infection, bleeding (7%) (6% severe anemia)	E D
Hepatobiliary	↑ ALT (7%) (2% severe)	E
	↑ Bilirubin (27%) (5% severe)	E
	Pancreatitis (1%)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (76%) (↓ Ca, K, or PO4; 16% severe)	E D
	Tumor lysis syndrome (2%)	E
Nervous System	Dysgeusia (10%)	E
Renal	Renal failure (<10%)	E
Respiratory	Dyspnea (9%)	E
	Pneumonitis (<10%)	E
	Pulmonary edema , hypoxia (2%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for enasidenib include nausea, vomiting, ↑ bilirubin, anorexia, severe ↓ Ca, K, or PO4, diarrhea, and fatigue.

Differentiation syndrome, which may be serious or fatal if not treated, has been reported. Symptoms may include the following: unexplained 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. Time of onset has been reported as early 1 day and up to 5 months after initiation of treatment.

Serious cases of noninfectious **leukocytosis** have occurred. The majority of cases had an onset during the first 3 months of treatment.

Hyperuricemia associated with **abnormal electrolyte changes**, consistent with signs and symptoms of **tumor lysis syndrome (TLS)**, has been reported. Time of onset was usually within the first 3 months of treatment.

Enasidenib may interfere with bilirubin metabolism through UGT 1A1 inhibition. It has caused dose-dependent **hyperbilirubinemia**, starting from the onset of treatment and stabilizing by the end of the first month. Patients with congenital UGT1A1 deficiency (Gilbert Syndrome) experienced a more rapid increase in bilirubin and more frequently experienced an increase > 3 x ULN.

Gastrointestinal adverse events were generally mild to moderate. Symptoms usually occurred during the first month of treatment and often resolved with continued treatment.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Treatment should be initiated following confirmation of IDH2 mutation through a validated test.

Adults:

Oral: 100 mg Daily

Dosage with Toxicity:

Dose Level	Enasidenib Dose (mg/day)
0	100
-1	50
-2	Discontinue

Toxicity	Action
Differentiation syndrome	If suspected, initiate systemic corticosteroids and hemodynamic monitoring. Hold enasidenib for severe pulmonary symptoms (requiring intubation or ventilator support) and/or renal dysfunction ≥ 48 hours after initiation of corticosteroids. Resume when toxicity ≤ Grade 2.
Noninfectious leukocytosis (WBC > 30 x 10^9/L)	Initiate hydroxyurea (per standard institutional practices). Hold enasidenib if leukocytosis does not improve with hydroxyurea. Resume when WBC < 30 x 10^9/L, at current dose.
Bilirubin > 3 x ULN for ≥ 2 weeks (without elevated transaminases or other hepatic disorders)	Decrease to 50 mg daily. Increase to 100 mg daily when bilirubin < 2 x ULN.
Other ≥ Grade 3 toxicity, including tumour lysis syndrome	Hold. Resume when toxicity ≤ Grade 2, at 50 mg daily; May increase to 100 mg daily when toxicity ≤ Grade 1. If ≥ Grade 3 toxicity recurs, discontinue.

Dosage with Hepatic Impairment:

Patients with hepatic impairment have not been studied; there are no specific dose adjustments recommended. Mild hepatic impairment does not have a clinically meaningful effect based on the covariate population pharmacokinetic (PK) analysis.

Starting dose adjustment is not recommended in patients with congenital UGT1A1 deficiency. Dose can be reduced for higher bilirubin levels.

Dosage with Renal Impairment:

Population PK analyses in patients with advanced hematologic malignancies, which included patients with mild or moderate renal impairment, identified no apparent relationship between renal function or serum creatinine levels and enasidenib exposure.

Creatinine Clearance (mL/min)	Enasidenib Dose
≥ 30	No dose adjustment required.
< 30	No data available.

Dosage in the elderly:

No dose adjustment is required in patients ≥ 65 years of age. In clinical studies, use in patients ≥ 65 years of age was not associated with differences in safety or efficacy.

Dosage based on gender:

The effects of gender on pharmacokinetics have not been formally studied; no clinically meaningful effects on pharmacokinetics based on gender were observed in population PK analysis.

Dosage based on ethnicity:

The effects of race on pharmacokinetics have not been formally studied; no clinically meaningful effects on pharmacokinetics based on race (White, Black or Asian) were observed in population PK analysis.

Children:

Safety and efficacy in children have not been established.

back to top

F - Administration Guidelines

- Enasidenib may be administered with or without food.
- Tablets should be swallowed whole with water and not chewed, crushed or split.
- If a dose is missed, patient may take the dose as soon as possible if within the same day, otherwise the dose should be skipped and the next dose should be taken as scheduled. Patients should not take 2 doses at the same time to make up for a missed dose.
- Store at room temperature (15 – 25°C) in the original bottle. Protect from moisture.

back to top

G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, or component of the container

Other Warnings/Precautions:

- Patients with congenital UGT1A1 deficiency (Gilbert Syndrome) should be monitored closely.
- Patients with severe renal impairment (CrCl < 30 mL/min) were excluded from clinical trials.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: No
- Mutagenicity: No
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
    - Enasidenib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **8 weeks** after the last dose. Enasidenib may affect the effectiveness of combined hormonal contraceptives.
    - Enasidenib and its metabolite can transfer through the blood placental barrier in animals.
- Excretion into breast milk: Unknown

    - Breastfeeding is not recommended during treatment, and for at least **8 weeks** after the last dose.
- Fertility effects: Probable
    - Histiopathologic changes in testes, epididymides and/or ovary have been observed in animal studies.

back to top

H - Interactions

Enasidenib is metabolized by multiple CYP enzymes (e.g., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and multiple UGTs (e.g., UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B15). The active metabolite, AGI-16903, is metabolized by multiple enzymes (e.g., CYP1A2, CYP2C19, CYP3A4, UGT1A1, UGT1A3, and UGT1A9).

In vitro, enasidenib and its active metabolite inhibit several enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and UGT1A1) and drug transporters (P-gp, BCRP, OAT1, OATP1B1, OATP1B3, and OCT2) and also induce CYP2B6 and CYP3A4.

AGENT	EFFECT	MECHANISM	MANAGEMENT
OATP1B1, OATP1B3 and BCRP substrates (i.e. rosuvastatin)	↑ substrate concentration and/or toxicity (increased rosuvastatin AUC by 3.5-fold)	Enasidenib is a OATP1B1, OATP1B3, and BCRP inhibitor	Monitor for clinical signs of toxicity. Adjust dose of substrates as clinically indicated.
P-glycoprotein substrates (i.e. digoxin)	↑ substrate concentration and/or toxicity (increased digoxin AUC by 1.2- fold)	Enasidenib is a P-gp inhibitor	Monitor for clinical signs of toxicity. Adjust dose of substrates with narrow therapeutic indices as clinically indicated.
Combined hormonal contraceptives	↑ or ↓ substrate concentration and/or toxicity (theoretical)		Clinical significance is unknown.

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC, including differential distribution	Baseline, every 2 weeks for at least 3 months, and as clinically indicated
Liver function tests	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Serum uric acid and electrolytes (including Ca, K, PO4)	Baseline, every 2 weeks for at least 3 months, and as clinically indicated
Clinical toxicity assessment for respiratory effects (including differentiation syndrome), infection, bleeding, and GI effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

K - References

Dittakavi S, Hallur G, Purra BR, Kiran V, Zakkula A, Mullangi R. Validated LC-MS/MS Method for Simultaneous Quantitation of Enasidenib and its Active Metabolite, AGI-16903 in Small Volume Mice Plasma: Application to a Pharmacokinetic Study. Drug Res (Stuttg). 2020 Jan;70(1):41-48.

Enasidenib. Lexicomp Inc. Accessed Feb 11, 2020.

Health Canada health professional risk communication: IDHIFA (enasidenib mesylate) – Market withdrawal and continued access. June 8, 2023.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Antiemesis: Version 1.2019, 2019.

Prescribing Information: Idhifa (enasidenib). Celgene Corporation, NJ. Nov 2020.

Product Monograph: Idhifa (enasidenib). Celgene Inc. Nov 30, 2020.

July 2023 Updated section A on enasidenib withdrawal from market

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and

expenses) arising from such person's use of the information in the Formulary.

back to top