PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr IDHIFA®

Enasidenib (as enasidenib mesylate)

50 mg, 100 mg Tablets for Oral Use

Antineoplastic

IDHIFA (enasidenib), indicated for the treatment of adult patients with relapsed or refractory Acute Myeloid Leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for IDHIFA please refer to Health Canada's Notice of Compliance with conditions - drug products web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php).

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November 30, 2020

Licensed from:
Agios Pharmaceuticals,
Cambridge, MA 02139

Submission Control No: 242218

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) for its indicated use.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

RECENT MAJOR LABEL CHANGES

- Serious Warnings and Precautions (3.0) 02/2020
- Warnings and Precautions, Respiratory, Differentiation Syndrome (7.0) 02/2020

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IDHIFA (enasidenib), indicated for the treatment of adult patients with relapsed or refractory Acute Myeloid Leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for IDHIFA please refer to Health Canada's Notice of Compliance with conditions - drug products web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php).

PART I: HEALTH PROFESSIONAL INFORMATION

NOC/c

1 INDICATIONS

IDHIFA® (enasidenib tablets) is indicated for:

- the treatment of adult patients with relapsed or refractory Acute Myeloid Leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation

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

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ *65* years of age): No dosage adjustment is required for IDHIFA based on age. No overall differences in safety or efficacy were observed between patients ≥65 years and patients younger than 65 years of age.

NOC/c

2 CONTRAINDICATIONS

IDHIFA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.**

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3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include unexplained fever, dyspnea, acute respiratory distress represented by dyspnea and/or hypoxia with need for supplemental oxygen, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction. Differentiation syndrome has been observed as early as 1 day and up to 5 months after initiation of IDHIFA. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. Hospitalization for close observation and monitoring of patients with pulmonary and / or renal manifestation is recommended (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

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4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of IDHIFA is 100 mg taken orally once daily with or without food until disease progression or unacceptable toxicity (see **Drug-Food Interactions**). It is recommended to treat patients for a minimum of 6 months to allow time for clinical response.

Health Canada has not authorized an indication for pediatric use (see **INDICATIONS**).

No dose adjustment is required for elderly patients (≥ 65 years of age) (see **WARNINGS AND PRECAUTIONS, Special Populations)**.

No dose adjustment is required for patients with renal impairment (CrCl > 30mL/min) (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**).

Instructions for dose interruptions and reductions for IDHIFA are outlined in the Table 1 below.

Table 1: Dose Modification Instructions for Toxicity

Adverse Reaction	Recommended Action
• Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring (see **WARNINGS AND PRECAUTIONS, General**). • 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 • Resume IDHIFA when signs and symptoms improve to Grade 2* or resolve.
• 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 severe, Grade 4 is life-threatening.

4.3 Administration

IDHIFA tablets are to be taken orally about the same time each day. Do not crush or split the tablet but swallow whole with water.

4.5 Missed Dose

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. Patients should not take two doses on the same day.

5 OVERDOSAGE

In the event of overdose, monitor patients for adverse reactions and provide appropriate supportive care. It is not known if enasidenib is removed by dialysis.

For management of a suspected drug overdose, contact a regional poison control centre or hospital emergency department.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 50 mg and 100 mg enasidenib (as enasidenib mesylate)	colloidal silicone dioxide, hydroxypropyl cellulose, hypromellose acetate succinate, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium starch glycolate, talc and titanium dioxide

The 50 mg tablets are pale yellow to yellow oval shaped, debossed “ENA” on one side and “50” on the other side.

The 100 mg tablets are pale yellow to yellow capsule shaped, debossed “ENA” on one side and “100” on the other side.

IDHIFA tablets are available in bottles of 30.

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7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Blood and Lymphatic System Disorder

Noninfectious Leukocytosis

IDHIFA can induce myeloid proliferation resulting in a rapid increase in white blood cell count without evidence of infection or clinical signs of differentiation syndrome (see **WARNINGS AND PRECAUTIONS, Respiratory, Differentiation Syndrome**). In the pooled Phase 1/2 clinical trial, 13.6% of patients were reported with a treatment emergent adverse event (TEAE) of noninfectious leukocytosis with 6.5% of cases reported as serious. The majority of cases occurred within the first 3 months of treatment. Non-infectious leukocytosis led to dose interruption in 1.9% of patients and treatment discontinuation in 0.9% of patients (see **DOSAGE AND ADMINISTRATION**, and **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Metabolism and Nutrition Disorders

Tumor Lysis Syndrome

An increase in uric acid associated with imbalance in electrolytes, consistent with signs and symptoms of tumor lysis syndrome (TLS), has been observed. A TEAE of TLS was reported in 6.1% of patients of the pooled Phase 1/2 clinical trial with 4.7% of cases reported as serious. TLS usually occurred within the first 3 months of treatment. TLS led to treatment discontinuation in 0.9% of patients (see **DOSAGE AND ADMINISTRATION,** and **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Respiratory

Differentiation Syndrome

In the pooled Phase 1/2 clinical trial, 13.1% patients treated with IDHIFA experienced a TEAE of differentiation syndrome, which may be life-threatening or fatal if not treated. 7.5% of patients experienced differentiation syndrome that was reported as serious. Additionally, differentiation syndrome with fatal outcome has been reported outside of clinical trials related to a delay in recognition or to a delay in treatment initiation. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells. While there is no diagnostic test for differentiation syndrome, symptoms reported by more than 50% of patients included acute respiratory distress represented by dyspnea and/or hypoxia with need for supplemental oxygen, unexplained fever, pulmonary infiltrates and renal impairment. Less common symptoms may include pleural effusion, lymphadenopathy, bone pain, peripheral edema with rapid weight gain, and pericardial effusion. ALT or AST elevation has been observed.

Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, and 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**). Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

Prescribers should inform patients of the risk of differentiation syndrome. Patients will be given a Patient Wallet Card and a Companion Wallet Card in the IDHIFA carton. The cards list differentiation syndrome symptoms and provides a section for physician and/or hospital/centre contact information. The card is to be used in the event any of the symptoms of differentiation syndrome are observed. Prescribers should encourage patients to keep the Patient Wallet Card with them and share the Companion Card with a caregiver. The patient or caregiver should show this card to any new treating healthcare professionals.

Driving and Operating Machinery

No studies on the ability to drive and the use of machines have been performed. IDHIFA is unlikely to affect the ability to drive or operate machinery. As with any new medication patients should be advised to exercise caution when driving a vehicle or operating potentially dangerous machinery until they know how IDHIFA affects them.

Monitoring and Laboratory Tests

Assess complete blood counts, including differential distribution, 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, as appropriate (see **DOSAGE AND ADMINISTRATION**).

Monitor liver function for bilirubin changes at baseline and in regular intervals. Reduce IDHIFA dose for elevation of bilirubin greater than 3 times the upper limit of normal sustained for ≥ 2 weeks without elevated transaminases or other hepatic disorders (see **DOSAGE AND ADMINISTRATION**).

Sexual Health

Fertility
No reproductive toxicity study in animals has been conducted to assess the effect of enasidenib on fertility. However, repeat dose oral toxicity studies in rats revealed dose-dependent histopathologic changes in testes, epididymides and/or ovary, suggesting the potential for enasidenib-related effects on male and female fertility (see **NON-CLINICAL TOXICOLOGY, Reproductive Toxicity**).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies of IDHIFA in pregnant women. Based on animal embryo-fetal toxicity studies, IDHIFA may cause embryo-fetal harm when administered to pregnant women. Oral administration of enasidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality (post implantation loss or abortion) and alterations to growth (decreased mean fetal body weight and/or skeletal variation of sternebrae not ossified) starting at 0.1 times the steady state clinical exposure based on the AUC at the recommended human dose of 100 mg once daily. In both rats and rabbits, enasidenib and its metabolite, AGI-16903, were detected in fetal plasma indicating transfer through the blood placental barrier (see **NON-CLINICAL TOXICOLOGY**). Use IDHIFA during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. If a patient or partner becomes pregnant while taking IDHIFA, advise the patient of the potential risk to a fetus.

Females of child-bearing potential are advised to use effective contraception during treatment with IDHIFA and for 8 weeks after the last dose of IDHIFA. Males with female partners of child-bearing potential are advised to use effective contraception during treatment with IDHIFA and for 8 weeks after the last dose of IDHIFA. IDHIFA may affect the effectiveness of combined hormonal contraceptives (see **DRUG INTERACTIONS**).

Obtain a pregnancy test on females of child-bearing potential prior to starting treatment with IDHIFA. Discuss with the patient the best contraceptive method for them.

7.1.2 Breast-feeding

It is unknown whether enasidenib or its metabolites are excreted in human milk. Because many small molecule drugs are excreted in human milk and the potential for adverse reactions in nursing infants from enasidenib, women should be advised not to breastfeed during treatment with enasidenib and for 8 weeks after the last dose.

7.1.3 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies suggests that use in the geriatric population is not associated with differences in safety or effectiveness. No dosage adjustment is required for IDHIFA based on age (see **CLINICAL TRIALS**).

NOC/c

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety evaluation of single-agent IDHIFA is based on the pooled Phase 1/2 data from the clinical study, AG221-C-001. The most common adverse reactions (≥15%) as assessed as related to treatment by the investigator were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite (Table 3). The most frequent serious adverse reactions to IDHIFA were differentiation syndrome (7.5%), febrile neutropenia (4.2%), leukocytosis (3.7%), nausea (3.3%), dyspnea (2.8%), decreased appetite (1.9%), pyrexia (1.9%), and vomiting (1.9%).

Dose interruptions due to adverse reactions to IDHIFA were required for 20.6% of patients. The most common adverse reactions leading to dose interruption were differentiation syndrome (3.7%), dyspnea (1.4%), fatigue (1.4%), and leukocytosis (1.4%). Dose reductions due to adverse reactions to IDHIFA were required for 4.2% of patients, most commonly for peripheral sensory neuropathy (1.4%). Discontinuations due to adverse reactions were required for 4.2% of patients.

Elevated Bilirubin

IDHIFA may interfere with bilirubin metabolism through inhibition of UGT1A1 (see **ACTION AND CLINICAL PHARMACOLOGY**). IDHIFA caused dose dependent bilirubin elevation beginning from the first on treatment assessment and stabilizing by the end of first month of treatment. Elevated bilirubin led to dose reductions in 0.5% (1/214), and treatment interruption in 4.2% (9/214) of patients (see **DOSAGE AND ADMINISTRATION**).

Patients with congenital UGT1A1 deficiency (Gilbert Syndrome) who received IDHIFA experienced a more rapid increase in bilirubin values, as compared to patients without this mutation and more frequently experienced bilirubin increase > 3ULN. Starting dose adjustment is not recommended for patients with Gilbert's Syndrome. Dose can be reduced for higher bilirubin levels.

Gastrointestinal Disturbance

Adverse reactions such as nausea, diarrhea, vomiting, and other reactions such as dysgeusia and decreased appetite were usually mild to moderate in severity, did not lead to treatment discontinuation and only infrequently required dose reduction or interruption. These reactions were not dose related and generally occurred during the first month of treatment and often resolved with continued treatment.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety evaluation of single-agent IDHIFA is based on the pooled Phase 1/2 data from the clinical study AG221-C-001 in which 214 patients with relapsed or refractory AML with an IDH2 mutation were assigned to receive 100 mg daily. Some patients were dose escalated to 200 mg daily. The median duration of treatment with IDHIFA was 4.6 months (range 0.3 to 34.1).

Table 3 – Summary of All Adverse Reactions Reported in ≥ 10% and Grade 3-4 Adverse Reactions in ≥ 1% of the treated IDHIFA Relapsed or Refractory AML patients from the Phase 1/2 AG221-C-001 study as Assessed by the Investigator as Related to Treatment

Body System Adverse Reaction	**IDHIFA 100 mg** **N = 214** **(%)**	
	Any Grade	**Grade 3-4**
Blood and lymphatic system disorders	**47 (22.0)**	**27 (12.6)**
Anemia	14 (6.5)	12 (5.6)
Febrile Neutropenia	9 (4.2)	8 (3.7)
Leukocytosis	16 (7.5)	4 (1.9)
Thrombocytopenia	7 (3.3)	7 (3.3)
Gastrointestinal Disorders	**96 (44.9)**	**10 (4.7)**
Diarrhea	33 (15.4)	2 (0.9)
Nausea	59 (27.6)	5 (2.3)
Vomiting	37 (17.3)	2 (0.9)
General disorders and administration site conditions	**57 (26.6)**	**5 (2.3)**
Fatigue	31 (14.5)	2 (0.9)
Hepatobiliary disorders	**22 (10.3)**	**6 (2.8)**
Hyperbilirubinemia	16 (7.5)	4 (1.9)
Investigations	**95 (44.4)**	**28 (13.1)**

Alanine aminotransferase increase	15 (7.0)	4 (1.9)
Blood bilirubin increased	57 (26.6)	11 (5.1)
Neutrophil count decreased	5 (2.3)	3 (1.4)
Platelet count decreased	6 (2.8)	5 (2.3)
Metabolism and Nutrition Disorders	**64 (29.9)**	**13 (6.1)**
Decreased appetite	41 (19.2)	4 (1.9)
Hyperuricemia	12 (5.6)	3 (1.4)
Tumor lysis syndrome	5 (2.3)	4 (1.9)
Nervous System Disorders	**41 (19.2)**	**1 (0.5)**
Dysgeusia	22 (10.3)	0
Respiratory, thoracic and mediastinal disorders	**50 (23.4)**	**27 (12.6)**
Differentiation Syndrome	27 (12.6)	14 (6.5)
Dyspnea	20 (9.3)	9 (4.2)
Hypoxia	3 (1.4)	3 (1.4)
Pulmonary Edema	4 (1.9)	3 (1.4)

8.3 Less Common Clinical Trial Adverse Reactions

Adverse drug reactions as assessed by the investigator that occur in 1 to <10% IDHIFA treated patients, and which are reported in 2 or more patients receiving IDHIFA, not described elsewhere are:

Blood and Lymphatic System Disorders: disseminated intravascular coagulation

Cardiac Disorders: cardiac failure tachycardia

Gastrointestinal Disorders: abdominal distention, abdominal pain, abdominal pain upper, constipation, dry mouth, dyspepsia, gastritis, gastroesophageal reflux disease, stomatitis

General Disorders and Administration Site Conditions: asthenia, chills, mucosal inflammation, edema peripheral, pain, pyrexia

Hepatobiliary Disorders: cholestasis, jaundice

Infections and Infestations: sepsis

Injury, Poisoning and Procedural Complications: contusion, fall

Investigations: amylase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, electrocardiogram QT increased, gamma-glutamyltransferase increased, lipase increased, neutrophil count decreased, platelet count decreased, weight decreased, weight increased, white blood cell count decreased

Metabolism and Nutrition Disorders: dehydration, hyperglycemia, hyperphosphatemia, hypertriglyceridemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, bone pain, myalgia

Nervous System Disorders: dizziness, headache, neuropathy peripheral, paresthesia

Psychiatric Disorders: insomnia

Renal and Urinary Disorders: acute kidney injury, renal failure

Respiratory, Thoracic and Mediastinal Disorders: cough, epistaxis, interstitial lung disease, lung disorder, pleural effusion

Skin and Subcutaneous Tissue Disorders: alopecia, dry skin, erythema, night sweats, photosensitivity reaction, pigmentation disorder, pruritis, rash, rash maculo-papular, skin lesion

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Changes in selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 4.

Table 4 – New or Worsening Laboratory Abnormalities Reported all Grades (≥ 20%) and Grade 3-4 (≥ 5%) of Relapsed or Refractory AML patients from the Phase 1/2 AG221-C-001 study

	IDHIFA 100 mg N = 213*	
Lab Shift	**Any Grade** (%)	**Grade 3-4** (%)
Total bilirubin increased	82.2	16.9
Calcium decreased	75.6	8.5
Potassium decreased	42.3	16.0
Phosphorous decreased	28.4	8.1

*Includes abnormalities occurring up to 28 days after last IDHIFA dose, if new or worsened by at least one grade from baseline, or if baseline was unknown. The denominator varies based on data collected for each parameter (N = 213 except phosphorus N = 211)

9 DRUG INTERACTIONS

9.2 Overview

In vitro studies suggest that metabolism of enasidenib is mediated by multiple CYP enzymes, and by multiple UGTs (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

9.3 Drug-Drug Interactions

Effect of IDHIFA on Drug Metabolizing Enzymes:

In vitro studies suggest that enasidenib inhibits the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and UGT1A1. Enasidenib induces CYP2B6 and CYP3A4.

In vitro studies suggest that the metabolite AGI-16903 inhibits the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

Effect of IDHIFA on Drug Transporters:

In vitro studies suggest that enasidenib inhibits P-gp, BCRP, OAT1, OATP1B1, OATP1B3, and OCT2, but not MRP2 or OAT3.

In vitro studies suggest that the metabolite AGI-16903 inhibits BCRP, OAT1, OAT3, OATP1B1, and OCT2, but not P-gp, MRP2, or OATP1B3.

Upon initiation or discontinuation of IDHIFA in patients being treated with other medicinal products that are substrates of CYP enzymes, UGT1A1 (uridine diphosphate glucuronosyltransferase) or transporters and have narrow therapeutic index, monitoring of the expected effect or drug concentration (if warranted) of the other medicinal product is recommended and the individual dose may be adjusted as needed (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Co-administration of IDHIFA may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

Drug Interaction Studies:

In a drug/drug interaction study in patients with AML or MDS harboring an IDH2 mutation, the effects of coadministration of IDHIFA 100 mg (for 29 days) with a single dose of other products were (see Table 5):

- OATP1B1, OATP1B3, and BCRP Substrates: coadministration of IDHIFA with rosuvastatin increased rosuvastatin AUC by 3.5-fold;

- P-gp Substrates: coadministration of IDHIFA with digoxin increased digoxin AUC by 1.2-fold.

Table 5: Established or Potential Drug-Drug Interactions

Proper / Common Name	Source of Evidence	Substrate CYPs or Transport Proteins	Ratio with/without Enasidenib Change in AUC_{0-30} for Other Product (95% CI)	Ratio with/without Enasidenib Change in $AUC_{0-\infty}$ for Other Product (95% CI)	Ratio with/without Enasidenib Change in C_{max} for Other Product (95% CI)	Clinical Comment
Rosuvastatin 10 mg single dose	CT	OATP1B1, OATP1B3, and BCRP	3.5 (2.5, 4.9)	3.4 (2.6, 4.5)	4.7 (3.4, 6.4)	Coadministration of IDHIFA with OATP1B1, OATP1B3 and BCRP substrates, e.g. rosuvastatin, may increase the incidence and severity of adverse reactions of these substrates. Dosing of OATP1B1, OATP1B3 and BCRP substrates should be adjusted as recommended in the respective PM, as clinically indicated.
Digoxin 0.25 mg single dose	CT	P-gp	1.2 (0.9, 1.6)	---	1.3 (0.8, 1.9)	Coadministration of IDHIFA with P-gp substrates may increase the incidence and severity of adverse reactions of these substrates. Patients taking IDHIFA with P-gp substrates with narrow therapeutic indices should adjust the dose of the P-gp substrate and be observed for clinical signs of toxicity, as recommended in the respective PM.

AUC_{0-30} = area under the concentration time curve from 0 to 30 hours post-dose; $AUC_{0-\infty}$ = area under the concentration time curve from 0 to infinity post-dose; C_{max} = maximum concentration; CI = confidence interval; CT = clinical trial

9.4 Drug-Food Interactions

The impact of food on multiple doses (repeat doses) of IDHIFA has not been established.

Results from a single dose food effect study indicate that consumption of a high fat meal produces a 50% increase in exposure (AUC) and a 63% increase in maximal concentration (Cmax) of enasidenib compared to when administered under fasted conditions in healthy adult

subjects (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). Although the pivotal and supportive clinical trials have been conducted with IDHIFA in the fasting state the increased exposure of enasidenib when administered with food is not expected to be clinically relevant.

9.5 Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted.

9.6 Drug-Laboratory Test Interactions

No interactions have been identified.

NOC/c

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Enasidenib is a small molecule inhibitor of the isocitrate dehydrogenase 2 (IDH2) mutant enzyme. IDH2 mutations confer a gain of function, whereby the aberrant enzyme catalyzes the production of the oncogenic metabolite 2-hydroxyglutarate (2-HG). 2-HG induces a block of cell differentiation by inhibiting the activity of chromatic-modifying histone and DNA demethylases. Enasidenib targets the mutant IDH2 variants R140Q, R172S, and R172K at approximately 40-fold lower concentrations than the wild-type enzyme in vitro. Inhibition of the mutant IDH2 enzyme by enasidenib led to decreased 2-HG levels and induced myeloid differentiation in vitro and in vivo in human xenograft models of IDH2 mutated AML.

In patients with IDH2 mutated AML, enasidenib decreased 2 HG levels in blood, decreased the percentages of blasts in the bone marrow, and increased percentages of mature myeloid cells.

10.2 Pharmacodynamics

Cardiac Electrophysiology

The potential for QTc prolongation with IDHIFA was evaluated in an open-label study in patients with advanced haematological malignancies with an IDH2 mutation. Based on the QTc data for a single dose of 30 mg to 650 mg and multiple doses of 100 mg daily in the fasted state, no large mean changes in the QTc interval (> 20 ms) were observed following treatment with IDHIFA.

Results from an in vivo safety pharmacology study in dogs given a single oral dose of 75 or 300 mg/kg showed that there was a dose-dependent increase in heart rate which remained elevated for 24 hours post-dose. The durations of PR and QT intervals were reduced during the first 5 hours postdose with treatment-related increases in heart rates. Lengthening of QTcV interval (QT interval duration corrected for heart rate changes) was noted beginning approximately 12 hours after dosing and continued to lengthen up to 24 hours after dosing.

10.3 Pharmacokinetics

The pharmacokinetics of IDHIFA were studied in patients with advanced hematologic malignancies with an IDH2 mutation.

Table 6 – Summary of IDHIFA Pharmacokinetic Parameters in patients with advanced hematologic malignancies with an IDH2 mutation after multiple doses

	[a]C_{max}	[a]T_{max}	[b]$t_{½}$	[a]AUC_{0-24}	[b]CL/F	[b]V/F
100 mg multiple dose in patients	11.6 mcg/mL	2.15 h	190 h	258.506 mcg*h/mL	0.70 L/h	192 L

The mean value is shown for all parameters with the exception of T_{max} which is the median.
[a]Reported from the phase 2 portion of study AG221-C-001
[b]Based on population-based pharmacokinetics

Absorption: The peak plasma concentration (C_{max}) was 1.4 mcg/mL [% coefficient of variation (CV%) 43.3] after a single dose of 100 mg, and 11.6 mcg/mL (CV% 40.3) at steady state for 100 mg daily in patients with advanced hematologic malignancies. Steady-state plasma levels were reached within 29 days of once-daily dosing. Accumulation is approximately 9-11-fold when administered once daily.

The area under concentration time curve (AUC) of enasidenib increased in an approximately dose proportional manner from 50 mg (0.5 times approved recommended dose) to 450 mg (4.5 times approved recommended dosage) single daily dose in patients with advanced hematologic malignancies, but increased in a less than dose proportional manner after having received multiple doses at steady state.

The absolute bioavailability after 100 mg oral dose of enasidenib is approximately 57%. After a single oral dose, the median time to C_{max} (T_{max}) is 4 hours and is 2.15 hours at steady state in patients with advanced haematological malignancies.

Food Effect: Results from the single dose food effect study (AG221-C-002) indicated that consumption of a high fat, high calorie meal produces an approximately 50% increase in the extent of absorption (AUC) of enasidenib, and a 63% increase in the rate of absorption (Cmax) of enasidenib compared to that observed when administered under fasted conditions in healthy adult subjects.

Distribution: The mean volume of distribution (Vd) of enasidenib is 55.8L (CV%29) based on a single dose study in healthy subjects. The estimated apparent volume of distribution in patients with advanced hematologic malignancies based on population PK analysis is 192L. Human plasma protein binding of enasidenib is 98.5%, and that of its metabolite AGI-16903 is 96.6%, in vitro.

Metabolism: Enasidenib accounted for 89% of the radioactivity in circulation and AGI-16903, the N-dealkylated metabolite, represented 10% of the circulating radioactivity.

In vitro studies suggest that metabolism of enasidenib is mediated by multiple CYP enzymes (e.g., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), and by multiple UGTs (e.g., UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B15). Further metabolism of the metabolite AGI-16903 is also mediated by multiple enzymes (e.g., CYP1A2, CYP2C19, CYP3A4, UGT1A1, UGT1A3, and UGT1A9).

Elimination: Enasidenib has a terminal half-life of 190 hours in patients with advanced haematological malignancies and a mean total body clearance (CL/F) of 0.70L/hour (CV% 62.5) based on the results from the population PK analysis.

Of the dose of enasidenib excreted, 89% of it is eliminated in the feces and 11% in the urine. Unchanged enasidenib accounts for 34% of the radiolabelled drug excreted in the feces and 0.4% in the urine.

Special Populations and Conditions

The effects of hepatic and renal impairment, gender, age, or race on the pharmacokinetics of enasidenib have not been formally studied. No clinically meaningful effect of the pharmacokinetics of enasidenib was observed for the following covariates in the population PK analysis: gender, age (19 years to 100 years), race (White, Black or Asian), mild hepatic impairment [defined as total bilirubin ≤ upper limit of normal (ULN) and aspartate transaminase (AST) > ULN or total bilirubin 1 to 1.5 times ULN and any AST], and renal impairment (defined as creatinine clearance ≥ 30 mL/min by Cockcroft-Gault formula).

Pediatrics: No data are available on administration of IDHIFA to pediatric or adolescent patients (< 18 years of age).

Geriatrics: Population pharmacokinetic analyses performed with data from 395 patients (median age 65 years, range 19 to 100 years) identified no apparent relationship between age and enasidenib exposure.

Hepatic Insufficiency: A dedicated study in subjects with hepatic impairment has not been conducted with IDHIFA.

Renal Insufficiency: Population pharmacokinetic analyses in patients with advanced hematologic malignancies including patients with normal renal function (N=134), mild (N=123) or moderate (N=71) renal impairment identified no apparent relationship between enasidenib exposure and renal function or serum creatinine levels. No data are available for severe renal impairment patients (CrCl < 30 mL/min) as such patients were excluded from the clinical studies.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 – 25°C). Keep the bottle tightly closed. Store in the original package to protect from moisture.

PART II: SCIENTIFIC INFORMATION

IDHIFA (enasidenib), indicated for the treatment of adult patients with relapsed or refractory Acute Myeloid Leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for IDHIFA please refer to Health Canada's Notice of Compliance with conditions - drug products web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php).

13 PHARMACEUTICAL INFORMATION

Drug Substance

Common name: enasidenib mesylate

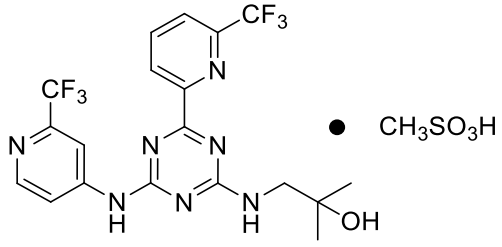
Chemical name: 2-methyl-1-((4-(6-(trifluoromethyl)pyridin-2-yl)-6-((2-(trifluoromethyl)pyridin-4-yl)amino)-1,3,5-triazin-2-yl)amino)propan-2-ol methanesulfonate (1:1)

Or

2-Propanol, 2-methyl-1-[[4-[6-(trifluoromethyl)-2-pyridinyl]-6-[[2-(trifluoromethyl)-4-pyridinyl]amino-1,3,5-triazin-2-yl]amino]-, methanesulfonate (1:1)

Molecular formula and molecular mass: $C_{19}H_{17}F_6N_7O \bullet CH_3SO_3H$ ($C_{20}H_{21}F_6N_7O_4S$), 569.48 g/mol

Structural formula:



Physicochemical properties: The drug substance is a white to off-white powder. The drug substance is practically insoluble (solubility ≤74µg/mL) in aqueous solutions across physiological pH range (pH 1.2 to 7.4). The pKa value is 2.22. The melting point is 216°C.

14 CLINICAL TRIALS

NOC/c

14.1 Trial Design and Study Demographics

The efficacy of IDHIFA in the treatment of patients with relapsed or refractory AML with an IDH2 mutation was evaluated from the phase 2 portion of the AG221-C-001 study. The Phase 2 study is an open-label, single-arm, international, multicentre clinical trial of 105 adult patients who received a 100-mg daily dose until disease progression or unacceptable toxicity. The IDH2 mutation was prospectively identified in all subjects. The Abbott RealTime™ IDH2 assay was used in the majority of patients. IDHIFA was given orally at a starting dose of 100 mg daily until disease progression or unacceptable toxicity. Adverse events were managed with dose reductions.

The baseline demographic and disease characteristics are shown in Table 7.

Table 7 – Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML with an IDH2 mutation from the Phase 2, AG221-C-001 study

Demographic and Disease Characteristics	**IDHIFA (100 mg daily) N=105**
Demographics	
Age (Years) Median (Min, Max)	68 (32, 89)
Age Categories, n (%)	
< 65 years	35 (33.3)
≥ 65 years	70 (66.7)
≥ 75 years	25 (23.8)
Sex, n (%)	
Male	63 (60.0)
Female	42 (40.0)
Race, n (%)	
White	78 (74.3)
Black	6 (5.7)
Native Hawaiian/ Other Pacific Islander	1 (1.0)
Not Provided	20 (19.0)
Disease Characteristics, n (%)	
ECOG PS, n (%)[a]	
0	24 (22.9)
1	64 (61.0)
2	16 (15.2)
Relapsed AML, n (%)	69 (65.7)
Primary Refractory AML, n (%)	36 (34.3)
IDH2 Mutation[b], n (%)	
R140	79 (75.2)
R172	26 (24.8)
Cytogenetic Risk Status, n (%)	
Intermediate	57 (54.3)
Poor	26 (24.8)
Missing /Failure	22 (21.0)
Prior Stem Cell Transplantation for AML, n (%)	17 (16.2)

Number of Prior Anticancer Regimens, n (%)[c]	
1	42 (40.0)
2	38 (36.2)
≥ 3	25 (23.8)
Median number of prior therapies (min, max)	2 (1, 5)

ECOG PS = *Eastern Cooperative Oncology Group Performance Status.*
[a] 1 patient had missing baseline ECOG PS.
[b] Based on results from central laboratories; the first 15 subjects underwent central laboratory testing at Brigham and Women's Hospital using a next-generation sequencing assay and the remaining subjects were tested using the Abbott Realtime IDH2 assay.
[c] Includes intensive and/or non-intensive therapies.

14.2 Study Results

The efficacy of single-agent IDHIFA is based on Phase 2 data from the clinical study, AG221-C-001. The primary efficacy endpoint was overall response rate (ORR). ORR was based on investigator assessment and was defined as the rate of responses, including complete remission (CR), CR with incomplete neutrophil recovery (CRi), CR with incomplete platelet recovery (CRp), partial remission (PR), and morphologic leukemia-free state (MLFS).

Secondary endpoints of the study included CR rate, CR+CRi/CRp rate, duration of response, overall survival (OS), and the rate of conversion from transfusion dependence to transfusion independence.

The efficacy results are shown in the following table 8. The median follow-up was 5.8 months (0.4, 22.5). Similar CR+CRi/CRp rates were observed in patients with either R140 or R172 mutation. Response was assessed by the investigator and retrospectively by an Independent Response Adjudication Committee (IRAC).

Table 8- Efficacy Results of Phase 2, AG221-C-001 Study in Relapsed or Refractory AML Patients

	IDHIFA (100 mg daily) Investigator Assessed	**IDHIFA (100 mg daily) Independent Response Adjudication Committee Assessed**
Endpoint	**Phase 2 N=105**	
CR[a] n (%) **95% CI[b]** **Median DOR[c] (months)** **95% CI[b]**	21 (20.0) (12.8, 28.9) 6.7 (3.7, 7.4)	18 (17.1) (10.5, 25.7) 6.5 (4.6, 9.2)
CRi /CRp[d] n (%) **95% CI[b]** **Median DOR[c] (months)** **95% CI[b]**	12 (11.4) (6.1, 19.1) 5.6 (1.0, NA)	10 (9.5) (4.7, 16.8) 5.6 (1.9, NA)
CR+CRi/CRp n (%) **95% CI[b]** **Median DOR[c] (months)** **95% CI[b]**	33 (31.4) (22.7, 41.2) 6.5 (3.7, 7.4)	28 (26.7) (18.5, 36.2) 6.5 (4.6, 9.2)
Overall Response Rate (CR + CRi + CRp + PR +MLFS), n (%) **95% CI[b]** **Median DOR (months)[c]** **95% CI[b]**	39 (37.1) (27.9, 47.1) 5.6 (3.7, 7.4)	33 (31.4) (22.7, 41.2) 6.5 (4.6, 9.2)
Specific Response Rates		
PR	4 (3.8)	3 (2.9)
MLFS	2 (1.9)	2 (1.9)
SD	44 (41.9)	62 (59.0)
PD	12 (11.4)	1 (1.0)
Summary of Overall Survival (OS)		
Number of events, n (%)	79 (75.2)	
Median duration of OS (months)	7.0	
95% CI[b]	(4.9, 8.8)	

AML = acute myeloid leukemia; CI: confidence interval; CR = complete remission; CRi = complete remission with incomplete neutrophil recovery; CRp = complete remission with incomplete platelet recovery; DOR = duration of response; MLFS = morphologic leukemia-free state; NA: not available; ORR = overall response rate; PD = progressive disease; PR = partial remission; SD = stable disease.

[a] CR (complete remission) was defined as <5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[b] 2-sided Exact Binomial 95% CI

[c] DOR (duration of response) was calculated as the date of the first documented response to the date of the first documented disease relapse, progression or death due to any cause, whichever is earlier. Estimates of median response duration are from an unstratified Kaplan-Meier analysis. Subjects missing response assessments are not included in any category.

[d] CRi/CRp (complete remission with incomplete hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (ANC < 1000/microliter / platelets <100,000/microliter).

The median time to first response (2.7 months) was shorter than the median time to best response (3.7 months) for ORR, indicating that responses can improve with continued treatment from the first evidence of response.

For subjects who achieved a best response of CR, 14.3% achieved a CR by Cycle 3, 57.1% by Cycle 5, and 95.2% achieved a CR by Cycle 7, indicating that in the absence of disease progression, subjects should be treated for at least 6 months.

Transfusion Outcomes

Of the 76 patients who were either red blood cell (RBC) and/or platelet transfusion dependent at baseline, 27 patients (35.5%) became both RBC and platelet transfusion independent during any 56-day postbaseline period. Additionally, 19 of the 29 patients (65.5%) who were both RBC and platelet transfusion independent at baseline remained both RBC and platelet transfusion independent during any 56-day postbaseline period.

Transfusion outcomes presented by baseline RBC and platelet transfusion status are summarized in Table 9.

Table 9 – Transfusion Dependence Status at Baseline Versus Treatment Transfusion Status

		Phase 2 Post-Baseline Transfusion Independence (N=105)	
Baseline Transfusion Status	**N**	**Independent [2]**	**Dependent**
Summary of RBC Transfusions			
		N (%)	**N (%)**
Dependent [1]	67	28 (41.8)	39 (58.2)
Independent	38	22 (57.9)	16 (42.1)
Summary of Platelet Transfusions			
Dependent [1]	59	21 (35.6)	38 (64.4)
Independent	46	32 (69.6)	14 (30.4)

1 = With at least one transfusion during the baseline period defined as 8 weeks prior to cycle 1, dose 1.

2 = Defined as no transfusion required for at least 56 consecutive days during the post baseline treatment period.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Repeat-Dose Toxicity

The toxicity profile of enasidenib was evaluated in repeat-dose oral toxicity studies of up to 90 days in rats and monkeys and 7 days in dogs following twice daily (BID) administration.

Rats: In rats, death or euthanasia in moribund conditions occurred at 100 mg/kg BID for up to 28 days of treatment. Doses of 30 and 10 mg/kg BID for 28 days and 20 and 5 mg/kg BID for 90 days were tolerated in rats. At ≥ 30 mg/kg BID, toxicities in several organs including gastrointestinal (GI) tract, liver, lung, lymphoid tissues, skeletal muscle, pancreas, kidney,

urinary bladder, adrenal gland, pituitary, salivary and mammary glands, bone (physis/cortex) and/or male and female reproductive organs were observed. Dose-related increases in bilirubin concentration were noted in the 14-, 28-, and 90-day studies at ≥ 10, ≥ 10 and 20 mg/kg BID respectively. In combination, GI tract atrophy/erosions, lymphoid atrophy, degeneration and necrosis, bone marrow hypocellularity and necrosis, skeletal muscle degeneration and necrosis, renal tubular vacuolation, adrenal cortical hemorrhage, and necrosis and epithelial vacuolation in pancreas contributed to death/moribundity at 100 mg/kg BID. In addition, rats receiving 30 and 100 mg/kg BID exhibited seminiferous tubule degeneration, hypospermia, and cellular debris in epididymal lumina in testes/epididymides, and decreased corpora lutea and increased atretic follicles in ovaries. At 30 mg/kg BID, severities and incidences of target organ toxicities were significantly lower compared to 100 mg/kg BID. At 20 and 5 mg/kg BID, target organ toxicities were limited to testes/epididymides and pancreas. Severities and incidences of histopathologic changes in testes/epididymides at 5 mg/kg BID were significantly lower than those observed at 20 mg/kg BID. Microscopic changes in the pancreas at ≤ 20 mg/kg BID were of low severity and incidence. The no-observed-adverse-effect level (NOAEL) in the 90-day toxicity study in rats was 5 mg/kg BID for males and 20 mg/kg BID for females with corresponding steady-state (ss) enasidenib exposures ($AUC_{0\text{-}24hr}$), approximately 0.10- and 1.4-fold, respectively, of the ss-$AUC_{0\text{-}24hr}$ at the recommended daily dose of 100 mg in humans.

Dogs: In dogs, mortality occurred at 50 mg/kg BID and doses of ≤ 15 mg/kg BID were tolerated. At ≥ 5 mg/kg BID, a series of cardiovascular effects including increased heart rate, decreased PR and RR intervals, prolongation of QTcV interval (50 mg/kg BID only), and arterial degeneration/necrosis in the heart were observed. Higher severities of these CV effects resulted in mortality at 50 mg/kg BID. Dose-related emesis, hypoactivity, cool to the touch, diarrhea, decreased food intake, dehydration, and increase in bilirubin concentration were also noted. At 15 mg/kg BID (maximum tolerated dose [MTD]), steady state enasidenib $AUC_{0\text{-}24hr}$ was approximately 0.05-fold of steady state clinical $AUC_{0\text{-}24hr}$ at the recommended daily dose.

Monkeys: In monkeys, 25 mg/kg BID for up to 7 days and 12 mg/kg BID for up to 28 days were euthanized in moribund condition associated with significant clinical signs, body weight loss/decreased bodyweight gain and decreased food consumption at both doses and ulcerative inflammation in the large intestine at 12 mg/kg BID only. Additional microscopic findings at 12 and 25 mg/kg BID included bone marrow hypercellularity, lymphoid depletion, neutrophilic infiltration and/or vacuolation in liver, adrenal gland and renal vacuolation, periarteritis in multiple organs, and/or physeal dysplasia in femur. Repeated doses of 2 to 8 mg/kg BID were tolerated in monkeys. At 8 mg/kg BID and/or lower doses, target organs of toxicity included lymphoid tissue/bone marrow hypocellularity and/or necrosis, vacuolation in adrenal gland and pancreas, cytoplasmic rarefaction in liver and/or decreased thickness/dysplasia in physis (femur/tibia). Findings at ≤ 6 mg/kg BID for 90 days were of low severities and incidences and considered to be secondary to enasidenib-related decrease in body weight/weight gain and food consumption. Dose-related increases in bilirubin concentration were noted in the 7-, 28-, and 90-day studies at ≥8, ≥5, and 12 mg/kg BID respectively. The NOAEL in the 90-day toxicity study in monkeys was 6 mg/kg BID with steady state enasidenib $AUC_{0\text{-}24hr}$, approximately 0.34-fold of steady state clinical $AUC_{0\text{-}24hr}$ at the recommended daily dose.

Carcinogenicity

Carcinogenicity studies have not been performed with enasidenib.

Genotoxicity
Enasidenib was not genotoxic. Enasidenib was not mutagenic in bacterial reverse mutation assays, and did not induce chromosomal aberrations in Chinese Hamster Ovary cells or micronuclei formation in polychromatic erythrocytes in bone marrow of rats administered single doses up to 2000 mg/kg.

Reproductive and Developmental toxicity
Fertility and early embryonic development toxicity studies in animals have not been conducted with enasidenib. However, repeat-dose oral toxicity studies in rats revealed dose-dependent histopathologic changes in male and female reproductive organs (testes, epididymides and ovary including: seminiferous tubule degeneration, hypospermia, and cellular debris in epididymal lumina in testes/epididymides, and decreased corpora lutea and increased atretic follicles in ovaries) suggesting potential effects on male and female fertility (see Repeat-dose Toxicity section).

Embryo-fetal toxicities in animals were observed at steady state exposure starting at 0.1 times of the clinical exposure determined at the recommended daily dose of 100 mg. Enasidenib administered orally to pregnant rats at a dose of 30 mg/kg twice daily during organogenesis (gestation days 6-17) was associated with maternal toxicity and adverse embryo-fetal effects including post-implantation loss, resorptions, decreased viable fetuses, lower fetal body weight, and sternebrae not ossified. These effects occurred in rats at approximately 1.6 times the clinical exposure based on the AUC at the recommended human daily dose of 100 mg/day. In pregnant rabbits treated during organogenesis (gestation days 7-19), enasidenib was maternally toxic at oral doses equal to 5 mg/kg/day or higher (exposure approximately 0.1 to 0.6 times the steady state clinical exposure at the recommended daily dose) and caused spontaneous abortions at 5 mg/kg/day (exposure approximately 0.1 times the steady state clinical exposure based on the AUC at the recommended daily dose). No fetal malformations were observed in enasidenib-treated rats and rabbits in embryo-fetal developmental studies.

In both rats and rabbits, enasidenib and its metabolite, AGI-16903, were detected in fetal plasma indicating their transfer through the blood placental barrier.

Phototoxicity:
Enasidenib did not induce phototoxicity in the in vitro Balb/c 3T3 mouse fibroblast assay.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

IDHIFA®
enasidenib tablets (as enasidenib mesylate)

Read this carefully before you start taking IDHIFA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about IDHIFA.

What is IDHIFA used for? See the following boxed text:

For the following indication IDHIFA has been approved *with conditions* (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

IDHIFA is used to treat Acute Myeloid Leukemia (AML) in adults with a particular change (mutation) in the enzyme "IDH2". AML is a form of cancer which affects your bone marrow and can cause problems with producing normal blood cells.

IDHIFA is used when your AML:

- has come back (relapsed) or,
- has not improved with another treatment (refractory).

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

Serious Warnings and Precautions

Differentiation Syndrome

Differentiation syndrome is a condition that affects your blood cells which may be life threatening or lead to death if not treated. Differentiation syndrome has happened within 1 day and up to 5 months after starting IDHIFA. Call your healthcare professional or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome while taking IDHIFA:

- fever
- cough
- shortness of breath
- swelling of arms and legs
- swelling around neck, groin, or underarm area
- fast weight gain (greater than 10 pounds within a week)
- bone pain
- dizziness or feeling lightheaded

If you develop any of these symptoms of differentiation syndrome, your healthcare professional may start you on a medicine called corticosteroids and may monitor you in the hospital.

You will be given a Patient Wallet Card and a Companion Wallet Card in the IDHIFA carton. The cards include space to record contact information for your healthcare professional and/or hospital/centre and lists Differentiation Syndrome signs and symptoms and treatment guidance. Keep the Patient Wallet Card with you at all times and share the Companion Card with a caregiver. You or your caregiver should show this card to any new healthcare professionals you see.

How does IDHIFA work?

Normal “IDH2” enzyme plays an important role in making energy for cells. Changes (mutations) in the enzyme in the bone marrow can cause cancers such as AML. These changes cause the bone marrow to stop producing normal blood cells that fight infection or stop bleeding. IDHIFA blocks the mutated “IDH2” enzyme. This increases the number of normal blood cells.

This medicine should only be used to treat AML with the “IDH2” mutation. Therefore, before starting treatment your doctor will test for this mutation.

It may take up to six months to see the full effect of IDHIFA on your AML.

Talk to your healthcare professional if you have any questions about how IDHIFA works or why this medicine has been prescribed for you.

What are the ingredients in IDHIFA?

Medicinal ingredients: enasidenib (as enasidenib mesylate)

Non-medicinal ingredients: colloidal silicone dioxide, hydroxypropyl cellulose, hypromellose acetate succinate, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium starch glycolate, talc and titanium dioxide

IDHIFA comes in the following dosage forms:
tablets: 50 mg or 100 mg

Do not use IDHIFA if:
You are allergic to enasidenib or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IDHIFA. Talk about any health conditions or problems you may have, including if you:
- are pregnant, or you or your partner are planning on becoming pregnant;
- are breastfeeding or planning to breastfeed. You should not breastfeed while taking IDHIFA and for 8 weeks after your last dose.

Your healthcare professional will do blood tests before you start taking IDHIFA and then every 2 weeks for at least the first 3 months to check for side effects.

Other warnings you should know about:

Pregnancy

You should not use IDHIFA during pregnancy. IDHIFA can cause harm to an unborn baby.
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before taking IDHIFA.
- If you are female and of an age where you could get pregnant, your healthcare professional will have you take a pregnancy test before you start treatment with IDHIFA.

Birth Control

If you are a **woman:**
- Do not become pregnant while you are taking IDHIFA and for 8 weeks after your last dose. This is because IDHIFA may cause harm to an unborn baby.
- You must use an effective method of birth control during treatment with IDHIFA and for 8 weeks after your last dose.
- IDHIFA may affect how hormonal birth control methods work and may cause them not to work as well. Talk to your healthcare professional about birth control methods that may be right for you while you are taking IDHIFA.

If you are a **man**:
- Your partner(s) must not become pregnant while you are taking IDHIFA and for 8 weeks after your last dose. This is because IDHIFA may cause harm to an unborn baby.
- You must use an effective method of birth control during treatment and for 8 weeks after your last dose.
- Talk to your healthcare professional about birth control methods that may be right for you while you are taking IDHIFA.

Fertility

IDHIFA may decrease your ability to have children. Talk to your healthcare professional for advice before taking it.

Driving and using machines

IDHIFA is not likely to affect you being able to drive, cycle or use any tools or machines. However, use caution until you know how IDHIFA affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitmains, minerals, natural supplements or alternative medicines.

How to take IDHIFA:

- Take this medicine by mouth.
- Do not chew, split or crush the tablets.
- Swallow the tablets whole with water.
- Take with or without food.

Usual adult dose: The recommended dose is 100 mg once a day.

Overdose:

If you think you have taken too much IDHIFA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget a dose of IDHIFA or vomit after taking a dose of IDHIFA, take the dose of IDHIFA as soon as posible on the same day then take your next dose the next day at your regularly scheduled time. Do not take 2 doses at the same time to make up for the missed dose.

What are possible side effects from using IDHIFA?

These are not all the possible side effects you may feel when taking IDHIFA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Decreased appetite
- Diarrhea
- Fatigue
- Nausea
- Vomiting
- Persistent, unpleasant, abnormal, or altered taste sensation

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Differentiation Syndrome: fever, cough, shortness of breath, swelling of arms and legs, swelling around neck,			√

groin, or underarm area, fast weight gain (greater than 10 pounds within a week), bone pain, dizziness, feeling lightheaded			
COMMON			
Decrease in red blood cells (anemia): tiredness, fatigue		√	
Decrease in white blood cells (febrile neutropenia): fever, chills or sweating, sore mouth, infections		√	
Increase in the number of white cells (leukocytosis): fever		√	
Decrease in platelets that help with blood clotting (thrombocytopenia): easy bruising, bleeding from gums or nose, prolonged bleeding from cuts		√	
Tumor lysis syndrome: lack of urination, severe muscle weakness, irregular heartbeat, seizures			√
Dyspnea: shortness of breath at rest, labored breathing			√
Low oxygen in your tissues (hypoxia): changes in the color of your skin, confusion, cough, fast heart rate, rapid breathing, shortness of breath, sweating, wheezing			√
Excess fluid in the lungs (pulmonary edema): difficulty breathing at rest or that worsens when lying down, chest pain, pink/red frothy mouth mucus			√
UNCOMMON			
Jaundice (elevated blood bilirubin): yellowing of the skin or whites of the eyes		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (15 - 25°C). Keep the bottle tightly closed. Store in the original package in order to protect from moisture.

Keep out of reach and sight of children.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use.

If you want more information about IDHIFA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://www.canada.ca/en/health-canada.html); the manufacturer's website www.celgene.ca, or by calling 1-877-923-5436.
- The information in this document is current as of the last revision date shown below.

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