Enasinib

Enasidenib 50 mg tablets

Everest

COMPOSITION

ENASINIB tablet: Each film coated tablet contains Enasidenib Mesylate INN equivalent to Enasidenib 50 mg.

PHARMACOLOGY

Mechanism of Action

Enasidenib is a small molecule inhibitor of the isocitrate dehydrogenase 2 (IDH2) enzyme. 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-hydroxyglutarate (2-HG) levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH2 mutated AML. In blood samples from patients with AML with mutated IDH2, enasidenib decreased 2-HG levels, reduced blast counts and increased percentages of mature myeloid cells.

Pharmacodynamics

Cardiac Electrophysiology The potential for QTc prolongation with enasidenib was evaluated in an open-label study in patients with advanced hematologic 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 Enasidenib.

Pharmacokinetics

The peak plasma concentration (Cmax) is 1.3 mcg/mL after a single dose of 100 mg, and 13 mcg/mL (CV% 46.3) at steady state for 100 mg daily. The area under concentration time curve (AUC) of enasidenib increases in an approximately dose proportional manner from 50 mg (0.5 times approved recommended dosage) to 450 mg (4.5 times approved recommended dosage) daily dose. Steady-state plasma levels are reached within 29 days of once-daily dosing. Accumulation is approximately 10-fold when administered once daily.

Absorption

The absolute bioavailability after 100 mg oral dose of Enasidenib is approximately 57%. After a single oral dose, the median time to Cmax (Tmax) is 4 hours.

Distribution

The mean volume of distribution of enasidenib is 55.8 L (CV% 29). Human plasma protein binding of enasidenib is 98.5% and of its metabolite AGI-16903 is 96.6% in vitro. Enasidenib is not a substrate for P-glycoprotein or BCRP, while AGI-16903 is a substrate of both Pglycoprotein and BCRP. Enasidenib and AGI-16903 are not substrates of MRP2, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2.

Elimination

Enasidenib has a terminal half-life of 137 hours (CV% 41) and a mean total body clearance (CL/F) of 0.74 L/hour (CV% 71).

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).

Specific Populations

No clinically meaningful effect on the pharmacokinetics of enasidenib was observed for the following covariates: 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], renal impairment (defined as creatinine clearance ≥30 mL/min by Cockcroft-Gault formula), sex, body weight (39 kg to 136 kg), and body surface area.

Drug Interaction Studies

In vitro studies suggest that Enasidenib inhibits the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and UGT1A1. Enasidenib inhibits P-gp, BCRP, OAT1, OATP1B1, OATP1B3, and OCT2, but not MRP2 or OAT3. 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. AGI-16903 inhibits BCRP, OAT1, OAT3, OATP1B1, and OCT2, but not P-gp, MRP2, or OATP1B3. Coadministration of Enasidenib may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

INDICATIONS AND USAGE

Enasidenib 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.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended starting dose of Enasidenib 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 Enasidenib tablets. Administer Enasidenib tablets orally about the same time each day. If a dose of Enasidenib 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.

Recommended Monitoring for Safety

Assess blood counts and blood chemistries for leukocytosis and tumor lysis syndrome prior to the initiation of Enasidenib and monitor at a minimum of every 2 weeks for at least the first 3 months during treatment. Manage any abnormalities promptly. Interrupt dosing or reduce dose for toxicities.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome

In the clinical trial, 14% of patients treated with Enasidenib 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 Enasidenib 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, and as early as 10 days and at up to 5 months after Enasidenib initiation.

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

SIDE EFFECTS
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 10 days and up to 5 months after starting Enasidenib. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome while taking Enasidenib:

- Fever
- Cough
- Shortness of Breath
- Swelling of Arms and Legs
- Swelling Around Neck, Groin, Or Underarm Area
- Fast Weight Gain
- Bone Pain

DRUG INTERACTION
In vitro studies suggest that Enasidenib inhibits the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and UGT1A1. Enasidenib inhibits P-gp, BCRP, OAT1, OATP1B1, OATP1B3, and OCT2, but not MRP2 or OAT3. 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. AGI-16903 inhibits BCRP, OAT1, OAT3, OATP1B1, and OCT2, but not P-gp, MRP2, or OATP1B3. Co-administration of Enasidenib may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

USE IN SPECIFIC POPULATIONS
Pregnancy
Based on animal embryo-fetal toxicity studies, Enasidenib can cause fetal harm when administered to a pregnant woman. There are no available data on Enasidenib use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal embryo-fetal toxicity studies, oral administration of Enasidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality and alterations to growth starting at 0.1 times the steady state clinical exposure based on the AUC at the recommended human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Lactation
There are no data on the presence of Enasidenib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because 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 Enasidenib and for at least 1 month after the last dose.

Females and Males of Reproductive Potential
Females
Advise females of reproductive potential to avoid becoming pregnant while receiving I Enasidenib. Advise females of reproductive potential to use effective contraception during treatment with Enasidenib and for at least 1 month after the last dose. Co-administration of Enasidenib may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

Males
Advise males with female partners of reproductive potential to use effective contraception during treatment with Enasidenib and for at least 1 month after the last dose of Enasidenib.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No dosage adjustment is required for Enasidenib based on age. In the clinical study, 61% of 214 patients were aged 65 years or older, while 24% were older than 75 years. No overall differences in effectiveness or safety were observed between patients aged 65 years or older and younger patients.

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED
ENASINIB tablet: Each HDPE container contains 30 tablets (each tablet contains 50 mg Enasidenib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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