IVOSENIB

Ivosidenib 250 mg tablets

Everest

COMPOSITION

IVOSENIB tablet: Each film coated tablet contains Ivosidenib INN 250 mg.

PHARMACOLOGY

Mechanism of Action

Ivosidenib is a small molecule inhibitor that targets the mutant isocitrate dehydrogenase 1 (IDH1) enzyme. In patients with AML, susceptible IDH1 mutations are defined as those leading to increased levels of 2-hydroxyglutarate (2-HG) in the leukemia cells and where efficacy is predicted by 1) clinically meaningful remissions with the recommended dose of Ivosidenib and/or 2) inhibition of mutant IDH1 enzymatic activity at concentrations of Ivosidenib sustainable at the recommended dosage according to validated methods. The most common of such mutations in patients with AML are R132H and R132C substitutions.

Ivosidenib was shown to inhibit selected IDH1 R132 mutants at much lower concentrations than wild-type IDH1 in vitro. Inhibition of the mutant IDH1 enzyme by Ivosidenib led to decreased 2HG levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH1-mutated AML. In blood samples from patients with AML with mutated IDH1, Ivosidenib decreased 2-HG levels ex-vivo, reduced blast counts, and increased percentages of mature myeloid cells. In a patient-derived xenograft intra-hepatic cholangiocarcinoma mouse model with IDH1 R132C, Ivosidenib reduced 2-HG levels.

Pharmacokinetics

The following Ivosidenib pharmacokinetic parameters were observed following administration of Ivosidenib 500 mg as a single dose or daily dose (for steady-state), unless otherwise specified. The steady-state pharmacokinetics of Ivosidenib 500 mg were comparable between patients with newly diagnosed AML, relapsed or refractory AML, and cholangiocarcinoma.

In patients with AML, the mean (%CV) peak plasma concentration (Cmax) is 4,503 ng/mL (38%) after a single dose, and 6,551 ng/mL (44%) at steady-state. The mean steady-state area under the concentration time curve (AUC) is 117,348 ng•hr/mL (50%). In patients with cholangiocarcinoma, the mean Cmax is 4,060 ng/mL (45%) after a single dose, and 4,799 ng/mL (33%) at steady-state. The mean steady-state AUC is 86,382 ng•hr/mL (34%).

Absorption

The median time to Cmax is approximately 3 hours in patients with AML and 2 hours in patients with cholangiocarcinoma.

Effect of Food

Following administration of a single dose in healthy subjects, a high-fat meal (approximately 900 to 1,000 calories, 500 to 600 fat calories, 250 carbohydrate calories and 150 protein calories) increased Ivosidenib Cmax by 98% (90% CI: 79%, 119%) and AUCinf by approximately 25%.

Distribution

The mean (%CV) apparent central volume of distribution (Vc/F) of Ivosidenib at steady-state is 234 L (47%) in patients with AML and 222 L (26%) in patients with cholangiocarcinoma. Protein binding of Ivosidenib ranges from 92 to 96% in vitro.

Elimination

In patients with AML, the mean (%CV) apparent clearance (CL/F) of Ivosidenib at steady state is 5.6 L/hour (35%) with a mean terminal half-life of 58 hours (42%). In patients with cholangiocarcinoma, the mean apparent clearance of Ivosidenib at steady state is 6.1 L/hour (31%) with a mean terminal half-life of 129 hours (102%).

Metabolism

Ivosidenib is the predominant component (>92%) of total radioactivity in plasma. Ivosidenib is primarily metabolized by CYP3A4 with minor contributions by N-dealkylation and hydrolytic pathways.

Excretion

After a single oral administration of radiolabeled Ivosidenib to healthy subjects, 77% of Ivosidenib was eliminated in the feces (67% as unchanged) and 17% in the urine (10% as unchanged).

Specific Populations

No clinically meaningful effects on the pharmacokinetics of Ivosidenib were observed based on age (18 years to 89 years), sex, race (White, Asian, Black or African American), body weight (38 to 150 kg), ECOG performance status, or mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m2, MDRD). The pharmacokinetics of Ivosidenib in patients with severe renal impairment (eGFR <30 mL/min/1.73m2, MDRD) or renal impairment requiring dialysis is unknown.

Patients with Hepatic Impairment

Following a single dose of Ivosidenib 500 mg, the geometric mean ratio (90% confidence interval) of Ivosidenib systemic exposure (AUC0-INF) in subjects with mild hepatic impairment (Child-Pugh A) was 0.85 (0.62, 1.15) and moderate hepatic impairment (Child-Pugh B) was 0.71 (0.48, 1.05) as compared to that in subjects with normal hepatic function. The pharmacokinetics of Ivosidenib in patients with severe hepatic impairment (Child-Pugh C) is unknown.

In vitro Studies

Metabolic Pathways

Ivosidenib may induce CYP2B6, CYP2C8, and CYP2C9 and therefore may affect the pharmacokinetics of sensitive substrates of these enzymes.

Drug Transporter Systems

Ivosidenib is a substrate for P-glycoprotein (P-gp). Ivosidenib is not a substrate for BCRP or hepatic transporters OATP1B1 and OATP1B3. Ivosidenib does not inhibit BCRP, OATP1B1, OATP1B3, OAT1, and OCT2 at clinically relevant concentrations. Ivosidenib is an inhibitor of OAT3 and P-gp.

INDICATIONS AND USAGE

Newly-Diagnosed Acute Myeloid Leukemia

Ivosidenib is indicated for the treatment of newly-diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

Relapsed or Refractory Acute Myeloid Leukemia

Ivosidenib is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

Locally Advanced or Metastatic Cholangiocarcinoma

Ivosidenib is indicated for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

DOSAGE AND ADMINISTRATION

Patient Selection

Acute Myeloid Leukemia

Select patients for the treatment of AML with Ivosidenib based on the presence of IDH1 mutations in the blood or bone marrow. Patients with AML without IDH1 mutations at diagnosis should be retested at relapse because a mutation in IDH1 may emerge during treatment and at relapse.

Locally Advanced or Metastatic Cholangiocarcinoma

Select patients for the treatment of locally advanced or metastatic cholangiocarcinoma with Ivosidenib based on the presence of IDH1 mutations.

Recommended Dosage

The recommended dose of Ivosidenib is 500 mg taken orally once daily until disease progression or unacceptable toxicity. Administer Ivosidenib with or without food. Do not administer Ivosidenib with a high-fat meal because of an increase in Ivosidenib. Do not split or crush Ivosidenib tablets. Administer Ivosidenib tablets orally about the same time each day. If a dose of Ivosidenib is vomited, do not administer a replacement dose; wait until the next scheduled dose is due. If a dose of Ivosidenib is missed or not taken at the usual time, administer the dose as soon as possible and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

Patients with Acute Myeloid Leukemia
For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response.

Patients with the Comorbidities of Severe Renal or Severe Hepatic Impairment
Treatment with Ivosidenib has not been studied in patients with pre-existing severe renal or hepatic impairment. For patients with pre-existing severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with Ivosidenib.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Differentiation Syndrome in AML
In the clinical trial, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with Ivosidenib experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with Ivosidenib included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor-lysis syndrome and creatinine increased. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of Ivosidenib. Differentiation syndrome occurred as early as 1 day and up to 3 months after Ivosidenib initiation and has been observed with or without concomitant leukocytosis.

QTc Interval Prolongation
Patients treated with Ivosidenib can develop QT (QTc) prolongation and ventricular arrhythmias. Of the 258 patients with hematological malignancies treated with Ivosidenib in the clinical trial (AG120-C-001), 9% were found to have a QTc interval greater than 500 msec and 14% of patients had an increase from baseline QTc greater than 60 msec. One patient developed ventricular fibrillation attributed to Ivosidenib. The clinical trial excluded patients with baseline QTc of ≥ 450 msec (unless the QTc ≥ 450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.

Guillain-Barré Syndrome
Guillain-Barré syndrome can develop in patients treated with Ivosidenib. Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with Ivosidenib in study AG120-C-001.

Monitor patients taking Ivosidenib for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue Ivosidenib in patients who are diagnosed with Guillain-Barré syndrome.

SIDE EFFECTS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Differentiation Syndrome in AML
- QTc Interval Prolongation
- Guillain-Barré Syndrome
- Fever
- Cough
- Trouble Breathing
- Rash
- Decreased Urination
- Dizziness or Lightheadedness
- Rapid Weight Gain
- Swelling of Your Arms or Legs

DRUG INTERACTIONS
Clinical Studies and Model-Based Approaches
Effect of Strong or Moderate CYP3A4 Inhibitors on Ivosidenib
Itraconazole was used as a strong CYP3A4 index inhibitor to evaluate the effect of CYP3A4 inhibition on the pharmacokinetics of Ivosidenib single-dose in a drug-drug interaction study in healthy subjects. Co-administration of 250 mg Ivosidenib with itraconazole (200 mg itraconazole once daily for 18 days) increased Ivosidenib single-dose AUC to 269% of control (90% CI: 245%, 295%) with no change in Cmax. In regards to multiple-dosing, note that because Ivosidenib induces the metabolism of CYP3A4 substrates following Ivosidenib multiple dosing, itraconazole (a CYP3A4 substrate) is not recommended to be used concomitantly with Ivosidenib in patients.

Effect of Strong CYP3A4 Inducers on Ivosidenib
Co-administration of Ivosidenib with a strong CYP3A4 inducer (600 mg rifampin once daily for 15 days) is predicted to decrease Ivosidenib steady-state AUC by 33%.

Effect of Ivosidenib on CYP3A4 Substrates
Ivosidenib induces CYP3A4, including its own metabolism. Co-administration of Ivosidenib with CYP3A4 substrates such as itraconazole is expected to decrease itraconazole steady-state AUC to a clinically relevant extent.

Effect of Gastric Acid Reducing Agents on Ivosidenib
Gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect Ivosidenib concentrations.

USE IN SPECIFIC POPULATIONS
Pregnancy
Based on animal embryo-fetal toxicity studies, Ivosidenib may cause fetal harm when administered to a pregnant woman. There are no available data on Ivosidenib 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 Ivosidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality and alterations to growth starting at 2 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.

Lactation
There are no data on the presence of Ivosidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with Ivosidenib and for at least 1 month after the last dose.

Pediatric Use
The safety and effectiveness of Ivosidenib in pediatric patients have not been established.

Geriatric Use
No overall differences in effectiveness or safety were observed between patients who were 65 years and older compared to 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
IVOSENIB tablet: Each HDPE container contains 60 film coated tablets (each tablet contains 250 mg Ivosidenib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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