Ascimib

Asciminib 40 mg tablets

Everest

COMPOSITION

ASCIMIB tablet: Each film coated tablet contains Asciminib Hydrochloride INN equivalent to Asciminib 40 mg.

PHARMACOLOGY

Mechanism of Action:

Asciminib is an ABL/BCR-ABL1 tyrosine kinase inhibitor. Asciminib inhibits the ABL1 kinase activity of the BCRABL1 fusion protein, by binding to the ABL myristoyl pocket. In studies conducted in vitro or in animal models of CML, asciminib showed activity against wild-type BCR-ABL1 and several mutant forms of the kinase, including the T315I mutation.

Pharmacokinetic properties

Asciminib steady-state exposure (AUC and Cmax) increase slightly more than dose proportional across the dose range of 10 to 200 mg (0.25 to 5 times the recommended 80 mg daily dosage) administered once or twice daily. Pharmacokinetic parameters are presented as geometric mean (CV%) unless otherwise stated.

Absorption

The median (range) Tmax of asciminib is 2.5 hours (2 to 3 hours).

Effect of food

The AUC and Cmax of asciminib decreased by 62% and 68%, respectively, with a high-fat meal (1000 calories, 50% fat) and by 30% and 35%, respectively, with a low-fat meal (400 calories, 25% fat) compared to the fasted state following administration of Asciminib.

Distribution

The apparent volume of distribution of Asciminib at steady state is 151 L (135%). Asciminib is the main circulating component in plasma (93% of the administered dose). Asciminib is 97% bound to human plasma proteins in vitro.

Elimination

The total apparent clearance of Asciminib is 6.7 L/hour (48%) at 40 mg twice daily and 80 mg once daily, and 4.1 L/hour (38%) at 200 mg twice daily. The terminal elimination half-life of Asciminib is 5.5 hours (38%) at 40 mg twice daily and 80 mg once daily, and 9.0 hours (33%) at 200 mg twice daily.

Metabolism

Asciminib is metabolized by CYP3A4-mediated oxidation, UGT2B7-and UGT2B17-mediated glucuronidation.

Specific Populations

No clinically significant differences in the pharmacokinetics of asciminib were observed based on sex, age (20 to 88 years), race (Asian 20%, White 70%, Black/African American 4%), or body weight (42 -184 kg), mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m2), or mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) to moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A Inhibitors: The Asciminib AUCinf and Cmax increased by 36% and 19%, respectively, following coadministration of a single Asciminib dose of 40 mg with a strong CYP3A4 inhibitor (clarithromycin). No clinically significant differences in the pharmacokinetics of Asciminib were observed when coadministered with itraconazole, which is also a strong CYP3A4 inhibitor.

Imatinib: The asciminib AUCinf and Cmax increase by 108% and 59%, respectively following coadministration of a single Asciminib dose of 40 mg with imatinib (an inhibitor of BCRP, CYP3A4, UGT2B17 and UGT1A3/4). The exposure changes are not considered clinically meaningful. Concomitant use of imatinib with Asciminib at 200 mg twice daily has not been fully characterized.

P-gp Substrates: Coadministration of Asciminib with a drug that is a substrate of P-gp may result in a clinically relevant increase in the plasma concentrations of P-gp substrates, where minimal concentration changes may lead to serious toxicities.

INDICATIONS AND USAGE

Asciminib is indicated for the treatment of adult patients with:

• Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs).

This indication is approved under accelerated approval based on major molecular response (MMR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

• Ph+ CML in CP with the T315I mutation.

DOSAGE AND ADMINISTRATION

Recommended Dosage in Patients with Ph+ CML-CP, Previously Treated with Two or More TKIs

The recommended dose of Asciminib is 80 mg taken orally once daily at approximately the same time each day or 40 mg twice daily at approximately 12-hour intervals. The recommended dose of Asciminib is taken orally without food. Avoid food consumption for at least 2 hours before and 1 hour after taking Asciminib. Continue treatment with Asciminib as long as clinical benefit is observed or until unacceptable toxicity occurs.

Recommended Dosage in Patients with Ph+ CML-CP with the T315I Mutation

The recommended dose of Asciminib is 200 mg taken orally twice daily at approximately 12-hour intervals. The recommended dose of Asciminib is taken orally without food. Avoid food consumption for at least 2 hours before and 1 hour after taking Asciminib.

Missed Dose

Once Daily Dosage Regimen: If a Asciminib dose is missed by more than approximately 12 hours, skip the dose and take the next dose as scheduled. Twice Daily Dosage Regimens: If a Asciminib dose is missed by more than approximately 6 hours, skip the dose and take the next dose as scheduled.

Dosage Modifications

Recommended Dosage Reductions for Asciminib for Adverse Reactions

Dosage for Patients with CP-CML, Previously Treated with Two or More TKIs is 40 mg once daily or, 20 mg twice daily. Permanently discontinue Asciminib in patients unable to tolerate 40 mg once daily or, 20 mg twice daily.

Dosage for Patients with Ph+ CML-CP with the T315I Mutation is 160 mg twice daily. Permanently discontinue Asciminib in patients unable to tolerate 160 mg twice daily.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelosuppression

Thrombocytopenia, neutropenia, and anemia have occurred in patients receiving Asciminib. Thrombocytopenia occurred in 98 of 356 (28%) patients receiving Asciminib, with Grade 3 or 4 thrombocytopenia reported in 24 (7%) and 42 (12%) of patients, respectively. Among the patients with Grade 3 or 4 thrombocytopenia, median time to first occurrence of events was 6 weeks (range, 0.1 to 64 weeks). Of the 98 patients with thrombocytopenia, 7 (2%) patients permanently discontinued Asciminib while Asciminib was temporarily withheld in 45 (13%) patients due to the adverse reaction.

Pancreatic Toxicity
Pancreatitis occurred in 9 of 356 (2.5%) patients receiving Asciminib, with Grade 3 pancreatitis occurring in 4 (1.1%) patients. All cases of pancreatitis occurred in the Phase I study (X2101). Of the 9 patients with pancreatitis, two (0.6%) patients permanently discontinued Asciminib, while Asciminib was temporarily withheld in 4 (1.1%) patients due to the adverse reaction. Asymptomatic elevation of serum lipase and amylase occurred in 76 of 356 (21%) patients receiving Asciminib, with Grade 3 and Grade 4 pancreatic enzyme elevations occurring in 36 (10%) and 8 (2.2%) patients, respectively. Of the 76 patients with pancreatic enzymes elevated, Asciminib was permanently discontinued in 7 (2%) patients due to the adverse reaction.

Hypertension
Hypertension occurred in 66 of 356 (19%) patients receiving Asciminib, with Grade 3 or 4 hypertension reported in 31 (9%) and 1 (0.3%) patients, respectively. Among the patients with Grade 3 or 4 hypertension, median time to first occurrence was 14 weeks (range, 0.1 to 156 weeks). Of the 66 patients with hypertension, Asciminib was temporarily withheld in 3 (0.8%) patients due to the adverse reaction.

Hypersensitivity
Hypersensitivity occurred in 113 of 356 (32%) patients receiving Asciminib, with Grade 3 or 4 hypersensitivity reported in 6 (1.7%) patients. Reactions included rash, edema, and bronchospasm. Monitor patients for signs and symptoms of hypersensitivity and initiate appropriate treatment as clinically indicated; for Grade 3 or higher hypersensitivity, temporarily withhold, reduce dose, or permanently discontinue depending Asciminib depending on persistence of hypersensitivity.

Cardiovascular Toxicity
Cardiovascular toxicity (including ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions) and cardiac failure occurred in 46 (13%) and in 8 (2.2%) of 356 patients receiving Asciminib, respectively. Grade 3 cardiovascular toxicity was reported in 12 (3.4%) patients, while grade 3 cardiac failure was observed in 4 (1.1%) patients. Grade 4 cardiovascular toxicity occurred in 2 (0.6%) patients, with fatalities occurring in 3 (0.8%) patients. Permanent discontinuation of Asciminib occurred in 3 (0.8%) patients due to cardiovascular toxicity and in 1 (0.3%) patient due to cardiac failure, respectively. Cardiovascular toxicity occurred in patients with pre-existing cardiovascular conditions or risk factors, and/or prior exposure to multiple TKIs.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, Asciminib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of Asciminib to pregnant rats and rabbits during the period organogenesis caused adverse developmental outcomes including embryo-fetal mortality and malformations at maternal exposures (AUC) equivalent to or less than those in patients at the recommended doses. Advise pregnant women and females of reproductive potential of the potential risk to a fetus if Asciminib is used during pregnancy or if the patient becomes pregnant while taking Asciminib. Verify the pregnancy status of females of reproductive potential prior to starting treatment with Asciminib. Females of reproductive potential should use effective contraception during treatment with Asciminib and for 1 week after the last dose.

SIDE EFFECTS
The following clinically significant adverse reactions can occur with Asciminib and are discussed in greater detail in other sections of the labeling:
- Myelosuppression
- Pancreatic Toxicity
- Hypertension
- Hypersensitivity
- Cardiovascular Toxicity

Drug Interaction
Strong CYP3A4 Inhibitors: Asciminib is a CYP3A4 substrate. Concomitant use of Asciminib with a strong CYP3A4 inhibitor increases both the Asciminib Cmax and AUC, which may increase the risk of adverse reactions. Closely monitor for adverse reactions in patients treated with Asciminib at 200 mg twice daily with concomitant use of strong CYP3A4 inhibitors.

Itraconazole Oral Solution Containing Hydroxypropyl-β-cyclodextrin: Concomitant use of Asciminib with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin decreases Asciminib Cmax and AUC, which may reduce Asciminib efficacy. Avoid coadministration of Asciminib at all recommended doses with itraconazole oral solution containing hydroxypropyl-βcyclodextrin.

USE IN SPECIFIC POPULATIONS
Pregnancy: Based on findings from animal studies and the mechanism of action, Asciminib can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on Asciminib use in pregnant women to evaluate a drug associated risk.

Lactation: There are no data on the presence of Asciminib or its metabolites in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with Asciminib and for 1 week after the last dose.

Females and Males of Reproductive Potential
Based on findings from animal studies, Asciminib can cause embryo-fetal harm when administered to a pregnant woman.

Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to starting treatment with Asciminib.

Contraception: Females of reproductive potential should use effective contraception during treatment with Asciminib and for 1 week after the last dose.

Infertility Females: Based on findings in animals, Asciminib may impair fertility in females of reproductive potential. The reversibility of the effect on fertility is unknown.

Pediatric Use: The safety and efficacy of Asciminib in pediatric patients have not been established.

Geriatric Use: No differences in safety or efficacy of Asciminib were observed between patients 65 years of age or older compared to younger patients. There is an insufficient number of patients 75 years of age or older to assess whether there are differences in safety or efficacy.

PHARMACEUTICAL INFORMATION
Storage Condition
Store at or below 25°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED
ASCIMIB tablet: Each HDPE container contains 30 film coated tablets, a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
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