Pemitinib

Pemigatinib INN

Everest

COMPOSITION

PEMITINIB 4.5 tablet: Each film coated tablet contains Pemigatinib INN 4.5 mg.

PEMITINIB tablet: Each film coated tablet contains Pemigatinib INN 13.5 mg.

DESCRIPTION

Pemigatinib is a kinase inhibitor with the chemical name 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one. Pemigatinib has a molecular formula of $C_{24}H_{27}F_2N_5O_4$ and molecular mass of 487.5 g/mole.

PHARMACOLOGY

Pemigatinib is a small molecule kinase inhibitor that targets FGFR1, 2 and 3 with IC_{50} values of less than 2nM. Pemigatinib also inhibits FGFR4 in vitro at a concentration approximately 100 times higher than those that inhibit FGFR1, 2, and 3. Pemigatinib inhibits FGFR1-3 phosphorylation and signaling and decreased cell viability in cancer cell lines with activating FGFR amplifications and fusions that results in constitutive activation of FGFR signaling. Constitutive FGFR signaling can support the proliferation and survival of malignant cells.

Pharmacodynamics

Serum Phosphate

Pemigatinib increases serum phosphate levels as a consequence of FGFR inhibition. Serum phosphate increases with increasing exposure across the dose range of 1 to 20 mg once daily, with increased risk of hyperphosphatemia with higher Pemigatinib exposure.

Cardiac Electrophysiology

At a dose 1.5 times the maximum recommended dose, Pemigatinib does not result in a large mean increase (i.e. > 20 ms) of the QTc interval.

Pharmacokinetics

The geometric mean (CV%) steady-state Pemigatinib $AUC_{0\text{-}24h}$ was 2620 nM-h (54%) and C_{max} was 236 nM (56%) for 13.5 mg orally once daily. Steady state Pemigatinib concentrations increases proportionally over the dose range of 1 to 20 mg (0.07 to 1.5 times the recommended dose). Steady-state is achieved within 4 days and Pemigatinib accumulates with a median accumulation ratio of 1.63 (range 0.63 to 3.28) following repeated once daily dosing.

Absorption

The median time to achieve peak Pemigatinib plasma concentration (T_{max}) is 1.13 (0.50-6.00) hours.

Effect of Food

Administration of Pemigatinib with a high-fat and high-calorie meal (approximately 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500-600 calories from fat) had no clinically significant effect on Pemigatinib pharmacokinetics.

Distribution

The estimated apparent volume of distribution is 235 L (60.8%) following a 13.5 mg oral dose. Protein binding of Pemigatinib is 90.6% and is independent of concentration in vitro.

Elimination

The geometric mean (%CV) elimination half-life (t½) of Pemigatinib is 15.4 (51.6%) hours and the geometric mean apparent clearance (CL/F) is 10.6 L/h (54%).

Metabolism

Pemigatinib is predominantly metabolized by CYP3A4 in vitro. The major drug-related moiety in plasma is unchanged Pemigatinib.

Excretion

Following a single oral 11 mg dose of radiolabeled Pemigatinib, 82.4% of the dose is recovered in feces (1.4% as unchanged) and 12.6% in urine (1% as unchanged).

Specific Populations

No clinically significant differences in the systemic exposure of Pemigatinib were observed based on age (21 - 79 years), sex, race/ethnicity (White 68.2%, Asian 16%, Black 6.3%, Hispanic 6%, other 3.5%) or body weight (39.8 - 156 kg).

Patients with Renal Impairment

No clinically significant differences in the systemic exposure of Pemigatinib were observed in mild to moderate renal impairment (eGFR 30 to 89 mL/min, MDRD) or end-stage renal disease (eGFR <15 mL/min/1.73 m^2) on intermittent hemodialysis.

Patients with Hepatic Impairment

No clinically significant differences in the systemic exposure of Pemigatinib were observed in mild (total bilirubin > upper limit of normal [ULN] to 1.5 × ULN or AST > ULN) to moderate (total bilirubin >1.5–3 × ULN with any AST) hepatic impairment.

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

CYP3A Inhibitors

Itraconazole (strong CYP3A inhibitor) increased C_{max} by 17% and increased AUC by 88% following a single oral Pemigatinib dose of 4.5 mg. Concomitant use of moderate CYP3A inhibitors is predicted to increase Pemigatinib exposure by approximately 50-80%.

CYP3A Inducers

Rifampin (strong CYP3A inducer) decreased Pemigatinib C_{max} by 62% and AUC by 85% following a single oral Pemigatinib dose of 13.5 mg. Concomitant use of a moderate CYP3A inducer is predicted to decrease Pemigatinib exposure by more than 50%.

Other Drugs

No clinically significant differences in Pemigatinib exposure when co-administered with Esomeprazole (proton pump inhibitor) or Ranitidine (histamine-2 antagonist).

In Vitro Studies

CYP Enzymes

Pemigatinib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 or an inducer of CYP1A2, CYP2B6, or CYP3A4.

Transporter Systems

Pemigatinib is a substrate of both P-gp and BCRP. P-gp or BCRP inhibitors are not expected to affect Pemigatinib exposure at clinically relevant concentrations. Pemigatinib is an inhibitor of P-gp, OCT2, and MATE1. Pemigatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine; this may occur due to inhibition of renal transporters OCT2 and MATE1 and may not affect glomerular function.

INDICATIONS AND USAGE

Pemigatinib is indicated for the treatment of-

Cholangiocarcinoma

Pemigatinib is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement

Pemigatinib is indicated for the treatment of adults with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement.

DOSAGE AND ADMINISTRATION

Pemigatinib should be taken with or without food at approximately the same time every day. Tablets should be swallowed whole. It shouldn't be crushed, chewed, splitted or dissolved into tablet.

Cholangiocarcinoma

The recommended dosage of Pemigatinib is 13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy, in 21-day cycles. Treatment should be continued until disease progression or unacceptable toxicity occurs.

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Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement
The recommended dosage of Pemigatinib is 13.5 mg orally once daily on a continuous basis. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Dosage Modification for Concomitant Use with Strong or Moderate CYP3A Inhibitors
Concomitant use of strong and moderate CYP3A inhibitors with Pemigatinib should be avoided. If concomitant use with a strong or moderate CYP3A inhibitor cannot be avoided:

- Pemigatinib dosage should be reduced from 13.5 mg to 9 mg.
- Pemigatinib dosage should be reduced from 9 mg to 4.5 mg.

Recommended Dosage for Severe Renal Impairment
The recommended dosage of Pemigatinib for patients with severe renal impairment (eGFR estimated by Modification of Diet in Renal Disease [MDRD] 15 mL/min/1.73 m2 to 29 mL/min/1.73 m2) is 9 mg with the schedule (intermittent or continuous) designated for the indication.

Recommended Dosage for Severe Hepatic Impairment
The recommended dosage of Pemigatinib for patients with severe hepatic impairment (total bilirubin > 3 × ULN with any AST) is 9 mg with the schedule (intermittent or continuous) designated for the indication.

CONTRAINDICATION
None.

WARNINGS AND PRECAUTIONS
Ocular Toxicity
Retinal Pigment Epithelial Detachment (RPED)
Pemigatinib can cause RPED, which may cause symptoms such as blurred vision, visual floaters, or photopsia.

For onset of visual symptoms, patients should be referred for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of Pemigatinib. Pemigatinib dose should be modified or permanently discontinued as recommended.

Dry Eye
Among 635 patients who received a starting dose of Pemigatinib 13.5 mg across clinical trials, dry eye occurred in 31% of patients, including Grade 3-4 in 1.6% of patients. Pemigatinib should be treated with ocular demulcents as needed.

Hyperphosphatemia and Soft Tissue Mineralization
Pemigatinib can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcification, calcinosis, and non-uremic calciphylaxis. Increases in phosphate levels are a pharmacodynamic effect of Pemigatinib.

Hyperphosphatemia should be monitored and initiated with a low phosphate diet when serum phosphate level is > 5.5 mg/dL. For serum phosphate levels > 7 mg/dL, phosphate lowering therapy should be initiated and withheld, Pemigatinib dose should be reduced or permanently discontinued based on the duration and severity of hyperphosphatemia.

Embryo-Fetal Toxicity
Based on findings in an animal study and its mechanism of action, Pemigatinib can cause fetal harm when administered to a pregnant woman. Oral administration of Pemigatinib to pregnant rats during the period of organogenesis caused fetal malformations, fetal growth retardation, and embryo-fetal death at maternal exposures lower than the human exposure based on area under the curve (AUC) at the clinical dose of 13.5 mg.

Pregnant women should be advised of the potential risk to the fetus. Males with female partners of reproductive potential should be advised to use effective contraception during treatment with Pemigatinib and for 1 week after the last dose.

SIDE EFFECTS
The most common side effects of Pemigatinib for cholangiocarcinoma include hair loss, diarrhea, nails separate from the bed or poor formation of the nail, feeling tired, change in sense of taste, nausea, constipation, mouth sores, dry eyes, dry mouth, decrease in appetite, vomiting, joint pain, stomach-area (abdominal) pain, low phosphate in blood, back pain, dry skin.

DRUG INTERACTIONS
Effect of Other Drugs on Pemigatinib
Strong and Moderate CYP3A Inducers
Concomitant use of Pemigatinib with a strong or moderate CYP3A inducer decreases Pemigatinib plasma concentrations, which may reduce the efficacy of Pemigatinib. Concomitant use of strong and moderate CYP3A inducers with Pemigatinib should be avoided.

Strong and Moderate CYP3A Inhibitors
Concomitant use of a strong or moderate CYP3A inhibitor with Pemigatinib increases Pemigatinib plasma concentrations, which may increase the incidence and severity of adverse reactions. Avoid concomitant use of strong and moderate CYP3A inhibitors with Pemigatinib. Reduce Pemigatinib dosage if concomitant use of strong and moderate CYP3A inhibitors cannot be avoided.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on the use of Pemigatinib in pregnant women. Pregnant women of the potential risk to a fetus should be avoided.

Lactation
There are no data on the presence of Pemigatinib or its metabolites in human milk or their effects on either the breastfed child or on milk production.

Females and Males of Reproductive Potential
Pemigatinib can cause fetal harm when administered to pregnant women.

Contraception
Females
Females of reproductive potential should be advised to use effective contraception during treatment with Pemigatinib and for 1 week after the last dose.

Males
Males with female partners of reproductive potential should be advised to use effective contraception during treatment with Pemigatinib and for 1 week after the last dose.

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

Geriatric Use
No overall differences in safety or effectiveness were observed between these patients and younger patients.

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

HOW SUPPLIED
PEMITINIB 4.5 tablet: Each HDPE container contains 14 film coated tablets, each of which contains Pemigatinib INN 4.5 mg, a silica gel desiccant and polyester coil with a child- resistant closure.

PEMITINIB tablet: Each HDPE container contains 14 film coated tablets, each of which contains Pemigatinib INN 13.5 mg, a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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