Selpacta

Selpercatinib INN

Composition:
Selpacta 40 Capsule: Each capsule contains Selpercatinib INN 40 mg.
Selpacta 80 Capsule: Each capsule contains Selpercatinib INN 80 mg.

Pharmacology:
Selpercatinib is a kinase inhibitor. Selpercatinib inhibited wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC50 values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, Selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable. In cellular assays, Selpercatinib inhibited RET at approximately 60-fold lower concentrations than FGFR1 and 2 and approximately 8-fold lower concentration than VEGFR3.

Indication:
Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
Selpercatinib is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC).
This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
RET-Mutant Medullary Thyroid Cancer
Selpercatinib is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.
This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
RET Fusion-Positive Thyroid Cancer
Selpercatinib is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).
This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Dosage and Administration:
Selpercatinib may be taken with or without food unless coadministrated with a proton pump inhibitor (PPI).

Recommended Dosage
The recommended dosage of Selpercatinib based on body weight is:
• Less than 50 kg: 120 mg
• 50 kg or greater: 160 mg
Take Selpercatinib orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity.
Swallow the capsules whole. Do not crush or chew the capsules.
Do not take a missed dose unless it is more than 6 hours until next scheduled dose.
If vomiting occurs after Selpercatinib administration, do not take an additional dose and continue to the next scheduled time for the next dose.

Contraindications:
Selpercatinib 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.

Warnings and Precautions:
Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.6% of patients treated with Selpercatinib. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).
Monitor ALT and AST prior to initiating Selpercatinib, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Selpercatinib based on the severity.
Hypertension
Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.
Do not initiate Selpercatinib in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Selpercatinib. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Selpercatinib based on the severity.
QT Interval Prolongation
Selpercatinib can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Selpercatinib has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.
Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Selpercatinib and during treatment.
Monitor the QT interval more frequently when Selpercatinib is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Selpercatinib based on the severity.
Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with Selpercatinib. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Selpercatinib, including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.
Permanently discontinue Selpercatinib in patients with severe or life-threatening hemorrhage.
Hypersensitivity
Hypersensitivity occurred in 4.3% of patients receiving Selpercatinib, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis.
If hypersensitivity occurs, withhold Selpercatinib and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Selpercatinib at a reduced dose and increase the dose of Selpercatinib by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Selpercatinib for recurrent hypersensitivity.
Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving Selpercatinib. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Adverse Reactions:
• Hepatotoxicity
• Hypertension
• QT Interval Prolongation
• Hemorrhagic Events
• Hypersensitivity
• Tumor Lysis Syndrome

Use in Specific Populations:
Pregnancy:
Based on findings from animal studies, and its mechanism of action, Selpercatinib can cause fetal harm when administered to a pregnant woman. There are no available data on Selpercatinib use in pregnant women to inform drug-associated risk. Administration of Selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation:
There are no data on the presence of Selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Selpercatinib and for 1 week after the final dose.
Females & Males of Reproductive potential:
Based on animal data, Selpercatinib can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily.

Pregnancy Testing:
Verify pregnancy status in females of reproductive potential prior to initiating Selpercatinib.

Contraception:
Females: Advise female patients of reproductive potential to use effective contraception during treatment with Selpercatinib and for 1 week after the final dose.
Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with Selpercatinib and for 1 week after the final dose.
Infertility: Selpercatinib may impair fertility in females and males of reproductive potential.

Pediatric Use:
The safety and effectiveness of Selpercatinib have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Selpercatinib for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. The safety and effectiveness of Selpercatinib have not been established in these indications in patients less than 12 years of age.
The safety and effectiveness of Selpercatinib have not been established in pediatric patients for other indications.

Drug Interactions:
Selpercatinib is a substrate of CYP3A4 and it is predominantly metabolized by CYP3A4. Coadministration of Selpercatinib with a moderate or strong CYP3A4 inhibitor may increase selpercatinib plasma concentrations, which may increase the risk of adverse reactions related to Selpercatinib, including QTc interval prolongation.Coadministration of Selpercatinib with a moderate or strong CYP3A4 inducer may decrease selpercatinib plasma concentrations.Coadministration of Selpercatinib with CYP3A4-sensitive substrates may increase plasma concentrations of the CYP3A4 substrates.Coadministration of Selpercatinib with sensitive CYP2C8 substrates may increase plasma concentrations of the CYP2C8 substrates.Selpercatinib inhibits the renal transporter multidrug and toxin extrusion protein 1 (MATE1). In vivo interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur. Selpercatinib may increase serum creatinine due to inhibition of the renal tubular secretion transporter MATE1, without affecting glomerular function.Selpercatinib is an in vitro substrate and inhibitor of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).Concomitant use of Selpercatinib with P-gp substrates increases their plasma concentrations,which may increase the risk of adverse reactions related to these substrates.

Overdose:
There is no known antidote for Selpercatinib. The treatment of overdose should consist of general supportive measures.

Storage:
Do not store above 25ºC. Protect from light. Keep out of the reach of children.

Packaging:
Selpacta 40 Capsule: Each HDPE container of Selpercatinib 40 contains 30 capsules, a silica gel desiccant and polyester coil with a child-resistant closure.
Selpacta 80 Capsule: Each HDPE container of Selpercatinib 80 contains 60 capsules, a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by:
ZISKA PHARMA **Ziska Pharmaceuticals Ltd.**
Kaliakoir, Gazipur, Bangladesh
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