Percanib
Tablet

DRUG INTERNATIONAL LTD.

Composition : Each capsule contains Selpercatinib INN 80mg.

Pharmacology : Selpercatinib is a kinase inhibitor. **Absorption:** The median tmax is 2 hours. The mean absolute bioavailability is 73% (60% to 82%) in healthy subjects. **Distribution:** The apparent volume of distribution (Vss/F) of selpercatinib is 191 L. Protein binding of selpercatinib is 96% in vitro and is independent of concentration. The blood-to-plasma concentration ratio is 0.7. **Elimination:** The apparent clearance (CL/F) is 6 L/h in patients and the half-life is 32 hours following oral administration in healthy subjects. **Metabolism:** It is metabolized predominantly by CYP3A4. Following oral administration of a single radiolabeled 160 mg dose of Selpercatinib to healthy subjects, unchanged Selpercatinib constituted 86% of the radioactive drug components in plasma. **Excretion:** Following oral administration of a single radiolabeled 160 mg dose of Selpercatinib to healthy subjects, 69% of the administered dose was recovered in feces (14% unchanged) and 24% in urine (12% unchanged).

Indications : • **RET Fusion-Positive Non-Small Cell Lung Cancer:** Selpercatinib is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA-approved test. • **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 medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy. • **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 thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). • **Other RET Fusion-Positive Solid Tumors:** Selpercatinib is indicated for the treatment of adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

Dosage and administration : The recommended dosage of Selpercatinib based on body weight is: i) Less than 50 kg: 120mg, ii) 50 kg or greater: 160mg. It may be taken with or without food unless coadministered with a proton pump inhibitor. It should be taken orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity, should swallow the capsules whole, should not crush or chew the capsules. If vomiting occurs after its administration, should not be taken an additional dose and continue to the next scheduled time for the next dose. **Dosage Modifications for Concomitant Use of Acid-Reducing Agents:** It should be avoided concomitant use of a PPI, a histamine-2 (H2) receptor antagonist, or a locally-acting antacid with Selpercatinib. If concomitant use cannot be avoided: • Selpercatinib should not be taken with food when coadministered with a PPI. • Selpercatinib should not be taken 2 hours before or 10 hours after administration of an H2 receptor antagonist. • Selpercatinib should not be taken 2 hours before or 2 hours after administration of a locally-acting antacid.

Dosage Modifications for Adverse Reactions:

Dose Reduction	Patients Weighing less than 50 kg	Patients Weighing 50 kg or greater
First	80mg orally twice daily	120mg orally twice daily
Second	40mg orally twice daily	80mg orally twice daily
Third	40mg orally once daily	40mg orally twice daily

Recommended Selpercatinib Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity	Grade 3 or Grade 4	• Selpercatinib should withhold and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. • Resume at reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence.
Hypertesion	Grade 3	• Selpercatinib should withhold for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	• Selpercatinib should discontinue.
QT Interval Prolongation	Grade 3	• Selpercatinib should withhold until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.
	Grade 4	• Selpercatinib should discontinue.
Hemorrhagic Events	Grade 3 or Grade 4	• Selpercatinib should with hold until recovery to baseline or Grade 0 or 1. • Selpercatinib should discontinue for severe or life threatening hemorrhagic events.
Hypersensitivity Reactions	All Grades	• Resume at a reduced dose by 3 dose levels while continuing corticosteroids. • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids.

Dose modification for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Current Selpercatinib Dosage	Recommended Selpercatinib Dosage	
	Moderate CYP3A Inhibitor	Strong CYP3A Inhibitor
120mg orally twice daily	80mg orally twice daily	40mg orally twice daily
160mg orally twice daily	120mg orally twice daily	80mg orally twice daily

Or, as directed by the registered physician.

Contraindication : It is contraindicated in patients with known hypersensitivity to Selpercatinib or any other components of this product.

Precautions : **Hepatotoxicity:** Serious hepatic adverse reactions can be occurred in patients treated with Selpercatinib. ALT and AST prior to initiating Selpercatinib should be monitored every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Selpercatinib should be withheld, dose should be reduced or permanently discontinued based on the severity. **Interstitial Lung Disease/Pneumonitis:** Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with Selpercatinib. Selpercatinib should be withheld and promptly investigated for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). **Hypertension:** Blood pressure should be optimized prior to initiating Selpercatinib. Blood pressure should be monitored after 1 week, at least monthly thereafter and as clinically indicated. Selpercatinib should be withheld, dose should be reduced or permanently discontinued based on the severity. **QT Interval Prolongation:** Selpercatinib can cause concentration-dependent QT interval prolongation. Patients should be monitored 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. **Hemorrhagic Events:** Selpercatinib should permanently discontinue in patients with severe or life-threatening hemorrhage **Hypersensitivity:** Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets. If hypersensitivity occurs, Selpercatinib should withhold and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Steroids should continue until patient reaches target dose and then taper. Selpercatinib should permanently discontinue for recurrent hypersensitivity. **Tumor Lysis Syndrome (TLS):** Patients should be closely monitored at risk of TLS, it should be considerd appropriate prophylaxis including hydration, and treat as clinically indicated. **Risk of Impaired Wound Healing:** Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Selpercatinib has the potential to adversely affect wound healing. Selpercatinib should withhold for at least 7 days prior to elective surgery. It should not be administerd for at least 2 weeks following major surgery and until adequate wound healing. **Hypothyroidism:** It should be treated with thyroid hormone replacement as clinically indicated. Selpercatinib should withhold until clinically stable or permanently discontinue based on severity.

Side effects : The most common side effects are Hepatotoxicity, Interstitial Lung Disease Hypertension, QT Interval Prolongation, Hemorrhagic Events, Hypersensitivity, Tumor Lysis Syndrome, Hypothyroidism and Risk of Impaired Wound Healing.

Use in pregnancy and lactation: It 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. Pregnant women should be advised of the potential risk to a fetus. **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, women should be advised not to breastfeed during treatment with Selpercatinib and for 1 week after the last dose. **Contraception : Females:** Females of reproductive potential should be advised to use effective contraception during treatment with Selpercatinib 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 Selpercatinib and for 1 week after the last dose.

Use in child : 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.

Drug interactions : • **Effects of Other Drugs on Selpercatinib: Acid-Reducing Agents:** Concomitant use of Selpercatinib with acid- reducing agents decreases its plasma concentrations. If coadministration cannot be avoided, Selpercatinib should be taken with food (with a PPI) or modify its administration time. **Strong and Moderate CYP3A Inhibitors:** Concomitant use of Selpercatinib with a strong or moderate CYP3A inhibitor increases its plasma concentrations, which may increase the risk of its adverse reactions, including QTc interval prolongation. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, the Selpercatinib dosage should be reduced and monitored the QT interval with ECGs more frequently. **Strong and Moderate CYP3A Inducers:** Concomitant use of Selpercatinib with a strong or moderate CYP3A inducer decreases its plasma concentrations, which may reduce its anti- tumor activity so it should be avoided. • **Effects of Selpercatinib on Other Drugs: CYP2C8 and CYP3A Substrates:** Selpercatinib is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of it with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. If coadministration cannot be avoided, recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling should be followed. **Certain P-gp Substrates:** Concomitant use of Selpercatinib with P-gp substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Coadministration of Selpercatinib with P-gp substrates should be avoided where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for P-gp substrates provided in their approved product labeling. • **Drugs that Prolong QT Interval:** Selpercatinib is associated with QTc interval prolongation. The QT interval with ECGs should be monitored more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

Overdose : There is no data available.

Storage : Store below 30°C in a cool & dry place, keep out of reach of children.

Packing : Each box contains 120 capsules in a container.