Reknib-100

Entrectinib INN 100 mg Capsule

Composition: Reknib-100 : Each capsule contains Entrectinib INN 100 mg.

Pharmacology: Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2, and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS1 (ROS1), and anaplastic lymphoma kinase (ALK) with IC50 values of 0.1 to 2 nM. Entrectinib also inhibits JAK2 and TNK2 with IC50 values > 5 nM. The major active metabolite of Entrectinib, M5, showed similar in vitro activity against TRK, ROS1, and ALK. Fusion proteins that include TRK, ROS1, or ALK kinase domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Entrectinib demonstrated in vitro and in vivo inhibition of cancer cell lines derived from multiple tumor types harboring NTRK, ROS1, and ALK fusion genes. Entrectinib demonstrated steady-state brain-to-plasma concentration ratios of 0.4 – 2.2 in multiple animal species (mice, rats, and dogs) and demonstrated in vivo anti-tumor activity in mice with intracranial implantation of TRKA-and ALK-driven tumor cell lines.

Pharmacokinetics: The pharmacokinetics for Entrectinib and its pharmacologically active major circulating metabolite M5 were characterized in adult patients with ROS1-positive NSCLC, NTRK gene fusion-positive solid tumors, and healthy subjects. The pharmacokinetics of Entrectinib and M5 are linear and are not dose-dependent or time-dependent. Steady state is achieved within one week for Entrectinib and two weeks for M5 following daily administration of Entrectinib. **Absorption:** The maximum Entrectinib plasma concentration is reached 4-6 hours after oral administration of a 600 mg dose. **Distribution:** Entrectinib and its active major metabolite M5 are both > 99% bound to human plasma proteins in vitro. **Metabolism:** Entrectinib is metabolized primarily by CYP3A4 (~76%). **Excretion:** After single oral dose of [14C]-labeled Entrectinib, 83% of radioactivity was excreted in feces (36% of the dose as unchanged Entrectinib and 22% as M5) with minimal excretion in urine (3%).

Indications:

•ROS1-Positive Non-Small Cell Lung Cancer: Entrectinib is indicated for the treatment of adult patients with metastatic non- small cell lung cancer (NSCLC) whose tumors are ROS1- positive.

•NTRK Gene Fusion- Positive Solid Tumors: Entrectinib is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that: • have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have either progressed following treatment or have no satisfactory alternative therapy.

Dosage and Administration:

•Recommended Dosage for ROS1-Positive Non- Small Cell Lung Cancer: The recommended dosage of Entrectinib is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity, Or, as directed by the registered physician.

•Recommended Dosage for NTRK Gene Fusion- Positive Solid Tumors: Adults: The recommended dosage of Entrectinib in adults is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity. Or, as directed by the registered physician.

Dosing in Pediatric Patients 12 Years and Older (Adolescents):

Body Surface Area (BSA)	Recommended Dosage (Orally Once Daily)
Greater than 1.50 m2	600 mg
1.11 to 1.50 m2	500 mg
0.91 to 1.10 m2	400 mg

Recommended Dose Reductions for Entrectinib Adverse Reactions:

Action	Adults and Pediatric Patients 12 Years and Older with BSA Greater than 1.50 m2 (Orally once daily)	Pediatric Patients 12 Years and Older with BSA of 1.11 to 1.50 m2 (Orally once daily)	Pediatric Patients 12 Years and Older with BSA of 0.91 to 1.10 m2 (Orally once daily)
First dose reduction	400 mg	400 mg	300 mg
Second dose reduction	200 mg	200 mg	200 mg

Dosage Modifications for Drug Interactions:

Adults and Pediatric Patients 12 Years and Older with BSA Greater than 1.50m2 : Coadministration of Entrectinib should avoid with moderate or strong CYP3A inhibitors. If coadministration cannot be avoided, Entrectinib dose should be reduced as follows:

- Moderate CYP3A Inhibitors: 200 mg orally once daily
- Strong CYP3A Inhibitors: 100 mg orally once daily

After discontinuation of a strong or moderate CYP3A inhibitor for 3 to 5 elimination half-lives, resume the Entrectinib dose that was taken prior to initiating the CYP3A inhibitor. If a patient misses a dose, patients should make up that dose unless the next dose is due within 12 hours. If a patient vomits immediately after taking a dose, patients should repeat that dose.

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

Precautions:
•**Congestive Heart Failure:** Left ventricular ejection fraction (LVEF) should be assessed prior to initiation of Entrectinib in patients with symptoms or known risk factors for CHF. Patients should be monitored for clinical signs and symptoms of congestive heart failure (CHF). For patients with myocarditis, with or without a decreased ejection fraction, MRI or cardiac biopsy may be required to make the diagnosis. Entrectinib dose should be reduced or permanently discontinued based on severity of CHF or worsening LVEF.
•**Central Nervous System (CNS) Effects:** CNS adverse reactions including cognitive impairment, mood disorders, dizziness, and sleep disturbances can occur with Entrectinib. Dose should withhold and then resume at same or reduced dose upon improvement or permanently discontinue Entrectinib based on severity.
•**Skeletal Fractures:** Entrectinib increases the risk of fractures. Promptly evaluate patients with signs or symptoms of fractures.

•**Hepatotoxicity:** Liver tests should be monitored including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter and as clinically indicated. Dose should withhold or permanently discontinue Entrectinib based on severity. If withheld, resume Entrectinib at same or reduced dose based on severity.
•**Hyperuricemia:** Serum uric acid levels should be assessed prior to initiation and periodically during treatment with Entrectinib. Patients should be monitored for signs and symptoms of hyperuricemia. Initiate treatment with uratelowering medications as clinically indicated and withhold Entrectinib for signs and symptoms of hyperuricemia. Resume at same or reduced dose upon improvement based on severity.
•**QT Interval Prolongation:** Patients should be monitored who have or who are at risk for QTc interval prolongation. QT interval and electrolytes should be assessed at baseline and periodically during treatment. Dose should be withheld and then resume at same or reduced dose, or permanently discontinue Entrectinib based on severity.
•**Vision Disorders:** Withhold for new visual changes or changes that interfere with activities of daily living until improvement or stabilization. Conduct an ophthalmological evaluation as appropriate. Resume at same or reduced dose upon improvement or stabilization.
•**Embryo-Fetal Toxicity:** Entrectinib can cause fetal harm. Females are advised of reproductive potential of the potential risk to a fetus and use of effective contraception.

Side Effects: The most common side effects are •fatigue, •constipation, •dysgeusia, •edema, •dizziness, •diarrhea, •nausea, •dysesthesia, •dyspnea, •myalgia, •cognitive impairment, •increased weight, •cough, •vomiting, •pyrexia, •arthralgia, and •vision disorders.

Use in Pregnancy and Lactation: Entrectinib can cause fetal harm when administered to a pregnant woman. There are no available data on Entrectinib use in pregnant women. Advise pregnant women of the potential risk to a fetus.
The pregnancy status should be verified of females of reproductive potential prior to initiating Entrectinib. Female patients of reproductive potential are advised to use effective contraception during treatment with Entrectinib and for at least 5 weeks following the final dose. Male patients with female partners of reproductive potential are advised to use effective contraception during treatment with Entrectinib and for 3 months following the final dose.
Lactation: There are no data on the presence of Entrectinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential adverse reactions in breastfed children from Entrectinib, lactating woman should be advised to discontinue breastfeeding during treatment with Entrectinib and for 7 days after the final dose.
Pediatric Use: The safety and effectiveness of Entrectinib in pediatric patients aged 12 years and older with solid tumors that have an NTRK gene fusion have been established.
The safety and effectiveness of Entrectinib in pediatric patients less than 12 years of age with solid tumors who have an NTRK gene fusion have not been established.
The safety and effectiveness of Entrectinib in pediatric patients with ROS1-positive NSCLC have not been established.

Drug Interactions:
•**Effect of Other Drugs on Entrectinib:**
Moderate and Strong CYP3A Inhibitors:
Adults and Pediatric Patients 12 Years and Older with BSA Greater than 1.50 m^2: Coadministration of Entrectinib with a strong or moderate CYP3A inhibitor increases its plasma concentrations, which could increase the frequency or severity of adverse reactions. So coadministration of strong or moderate CYP3A inhibitors with Entrectinib should be avoided. If coadministration is unavoidable, reduce the Entrectinib dose should be reduced.
Pediatric Patients 12 Years and Older with BSA Less Than or Equal to 1.50 m^2: Coadministration of Entrectinib with moderate or strong CYP3A inhibitors should be avoided. Grapefruit products during treatment with Entrectinib should be avoided as they contain inhibitors of CYP3A.
Moderate and Strong CYP3A Inducers: Coadministration of Entrectinib with a strong or moderate CYP3A inducer decreases its plasma concentrations, which may reduce its efficacy so it should be avoided.
Drugs That Prolong QT Interval: QT interval prolongation can occur with Entrectinib so it should be avoided.

Overdose: There is no data available.

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

Packaging: Reknib-100 : Each box contains 30 capsules in a container.

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