

Lotenib

Larotrectinib INN 100 mg Capsule

COMPOSITION

Lotenib-100: Each capsule contains Larotrectinib 100mg as Larotrectinib sulfate INN.

PHARMACOLOGY:

Mechanism of Action: Larotrectinib is an inhibitor of the tropomyosin receptor kinases (TRK), TRKA, TRKB, and TRKC. In a broad panel of purified enzyme assays, larotrectinib inhibited TRKA, TRKB, and TRKC with IC50 values between 5-11 nM. One other kinase TNK2 was inhibited at approximately 100-fold higher concentration. TRKA, B, and C are encoded by the genes NTRK1, NTRK2, and NTRK3. Chromosomal rearrangements involving in-frame fusions of these genes with various partner scan result in constitutively-activated chimeric TRK fusion proteins that can act as an oncogenic driver, promoting cell proliferation and survival in tumor cell lines.

Pharmacokinetics

Absorption: The mean absolute bioavailability of Larotrectinib capsules was 34% (range: 32% to 37%).

Distribution: The mean (CV%) volume of distribution (Vss) of Larotrectinib is 48 (38%) L following intravenous administration of Larotrectinib in healthy subjects. Larotrectinib is 70% bound to human plasma proteins in vitro and binding is independent of drug concentrations. The blood-to-plasma concentration ratio is 0.9.

Elimination: The mean (CV%) clearance (CL/F) of Larotrectinib is 98 (44%) L/h and the half-life is 2.9 hours following oral administration of Larotrectinib in healthy subjects.

Metabolism: Larotrectinib is metabolized predominantly by CYP3A4. Following oral administration of a single [¹⁴C] radiolabeled 100 mg dose of Larotrectinib to healthy subjects, unchanged Larotrectinib constituted 19% and an O-linked glucuronide constituted 26% of the major circulating radioactive drug components in plasma.

Excretion: Following oral administration of a single [¹⁴C] radiolabeled 100 mg dose of Larotrectinib to healthy subjects, 58% (5% unchanged) of the administered radioactivity was recovered in feces and 39% (20% unchanged) was recovered in urine.

INDICATIONS: Larotrectinib is indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine 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 no satisfactory alternative treatments or that have progressed following treatment.

DOSAGE AND ADMINISTRATION: Recommended Dosage in Adult and Pediatric Patients with Body Surface Area of at Least 1.0 Meter-Squared: The recommended dosage of Larotrectinib is 100 mg orally twice daily, with or without food, until disease progression or until unacceptable toxicity. **Recommended Dosage in Pediatric Patients with Body Surface Area Less Than 1.0 Meter-Squared:** The recommended dosage of Larotrectinib is 100 mg/m² orally twice daily, with or without food, until disease progression or until unacceptable toxicity. Whole capsules should be swallowed with water and the capsules should not be chewed or crushed. A missed dose should not be made up within 6 hours of the next scheduled dose. If vomiting occurs after taking a dose of Larotrectinib, the next dose should be taken at the scheduled time. Or, as directed by the registered physicians.

Dosage Modification for Adverse Reactions: Recommended Dosage Modifications for Larotrectinib for Adverse Reactions:

Dosage Modification	Adult and Pediatric Patients with Body Surface Area of at least 1.0 m ²	Pediatric Patients with Body Surface Area less than 1.0 m ²
First	75 mg orally twice daily	75 mg/m ² orally twice daily
Second	50 mg orally twice daily	50 mg/m ² orally twice daily
Third	100 mg orally once daily	25 mg/m ² orally twice daily

Larotrectinib should be permanently discontinued in patients who are unable to tolerate Larotrectinib after three dose modifications.

DRUG INTERACTIONS:

Effects of Other Drugs on Larotrectinib: Strong CYP3A4 Inhibitors: Coadministration of Larotrectinib with a strong CYP3A4 inhibitor may increase Larotrectinib plasma concentrations, which may result in a higher incidence of adverse reactions. Coadministration of Larotrectinib should be avoided with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If coadministration of strong CYP3A4 inhibitors cannot be avoided, Larotrectinib dose as recommended should be modified. **Strong CYP3A4 Inducers:** Coadministration of Larotrectinib with a strong CYP3A4 inducer may decrease Larotrectinib plasma concentrations, which may decrease the efficacy of Larotrectinib. Coadministration of Larotrectinib should be avoided with strong CYP3A4 inducers, including St. John's wort. If coadministration of strong CYP3A4 inducers cannot be avoided,

Larotrectinib dose as recommended should be modified.

Effects of Lotenib on Other Drugs: Sensitive CYP3A4 Substrates: Coadministration of Larotrectinib with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions. Coadministration of Larotrectinib should be avoided with sensitive CYP3A4 substrates. If coadministration of these sensitive CYP3A4 substrates cannot be avoided, patients for increased adverse reactions of these drugs should be monitored.

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

PRECAUTIONS:

Neurotoxicity: Among the 176 patients who received Larotrectinib, neurologic adverse reactions of any grade occurred in 53% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively. The majority (65%) of neurologic adverse reactions occurred within the first three months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurologic adverse reactions leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%). Patients and caretakers should be advised of these risks with Larotrectinib. Patients should be advised not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Larotrectinib should be withheld or permanently discontinued based on the severity. If withheld, Larotrectinib dosage should be modified when resumed.

Hepatotoxicity: Among the 176 patients who received Larotrectinib, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients. 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. Larotrectinib should be withheld or permanently discontinued based on the severity. If withheld, Larotrectinib dosage should be modified when resumed.

Embryo-Fetal Toxicity: Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, Larotrectinib can cause fetal harm when administered to a pregnant woman. Women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use an effective method of contraception during treatment and for 1 week after the final dose of Larotrectinib.

SIDE EFFECTS:

- Neurotoxicity
- Hepatotoxicity

USE IN PREGNANCY AND LACTATION: Larotrectinib can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on Larotrectinib use in pregnant women. Pregnant women should be advised of the potential risk to a fetus.

Lactation: There are no data on the presence of Larotrectinib or its metabolites in human milk and no data on its 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 Larotrectinib and for 1 week after the final dose.

Females and Males of Reproductive Potential:

Pregnancy Testing: Pregnancy status should be verified in females of reproductive potential prior to initiating Larotrectinib.

Contraception: Larotrectinib can cause embryo-fetal harm when administered to a pregnant woman.

Females: Female patients of reproductive potential should be advised to use effective contraception during treatment with Larotrectinib and for at least 1 week after the final dose.

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

Pediatric Use: The safety and effectiveness of Larotrectinib in pediatric patients was established based upon data from three multicenter, open-label, single-arm clinical trials in adult or pediatric patients 28 days and older.

Geriatric Use: Clinical studies of Larotrectinib did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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.

PACKING: Lotenib-100: Each box contains 10 capsule in blister pack.

Manufactured by
 **DRUG INTERNATIONAL LTD.**
Tongi, Gazipur, Bangladesh