Lotenib

Larotrectinib INN

DRUG INTERNATIONAL LTD.

Composition: Each capsule contains Larotrectinib INN 100 mg.

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 proteinsthat can act as an oncogenic driver, promoting cell proliferation and survival in tumor cell lines.

Pharmacokinetics

Absorption: The mean absolute bioavailability of Lotenib 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 Lotenib in healthy subjects.

Metabolism: Larotrectinib is metabolized predominantly by CYP3A4. Following oral administration of a single [^{14}C] 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 [^{14}C] 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: Lotenib 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 Lotenib 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 Lotenib 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 Lotenib, the next dose should be taken at the scheduled time. Or, as directed by the registered physicians.

Dosage Modifications: Recommended Dosage Modifications for Lotenib for Adverse Reactions:

Dosage Modification	Adultand Pediatric Patients with Body Surface Area of atleast 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

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

Side Effects:

- Neurotoxicity
- Hepatotoxicity

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

Use in Pregnancy and Lactation: Lotenib can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on Lotenib 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 Lotenib.

Contraception: Lotenib 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 Lotenib 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 Lotenib and for 1 week after the final dose.

Pediatric Use: The safety and effectiveness of Lotenib 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 Lotenib did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Drug Interactions:

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

Effects of Lotenib on Other Drugs: Sensitive CYP3A4 Substrates: Coadministration of Lotenib with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions. Coadministration of Lotenib 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.

Precautions:

Neurotoxicity: Among the 176 patients who received Lotenib, 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 Lotenib. Patients should be advised not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Lotenib should be withheld or permanently discontinued based on the severity. If withheld, Lotenib dosage should be modified when resumed.

Hepatotoxicity: Among the 176 patients who received Lotenib, 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. Lotenib should be withheld or permanently discontinued based on the severity. If withheld, Lotenib 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, Lotenib 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 Lotenib.

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: Each container contains 30 capsules in a box.