160 mm x 440 mm

Larogen

Larotrectinib Capsule

Larogen 25 Capsule: Each capsule contains Larotrectinib Sulfate INN equivalent to Larotrectinib 25 mg.

Larogen 100 Capsule: Each capsule contains Larotrectinib Sulfate INN equivalent to Larotrectinib 100 mg.

INDICATIONS AND USAGE

Solid Tumors

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

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.

Pediatric Patients with Body Surface Area Less Than 1.0 Meter-Squared.

The recommended dosage of Larotrectinib is 100 mg/m^2 orally twice daily, with or without food, until disease progression or until unacceptable toxicity.

Dosage Modifications for Adverse Reactions

For Grade 3 or 4 adverse reactions:

• Withhold Larotrectinib until adverse reaction resolves or improves to baseline or Grade 1. Resume at the next dosage modification if resolution occurs within 4 weeks.

• Permanently discontinue Larotrectinib if an adverse reaction does not resolve within 4 weeks.

The recommended dosage modifications for Larotrectinib for adverse reactions are provided in Table 1.

Table 1. 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

Permanently discontinue Larotrectinib in patients who are unable to tolerate Larotrectinib after three dose modifications.

Dosage Modifications for Coadministration with Strong CYP3A4 Inhibitors

Avoid coadministration of strong CYP3A4 inhibitors with Larotrectinib. If coadministration of a strong CYP3A4 inhibitor cannot be avoided, reduce the Larotrectinib dose by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Larotrectinib dose taken prior to initiating the CYP3A4 inhibitor.

Dosage Modifications for Coadministration with Strong CYP3A4 Inducers

Avoid coadministration of strong CYP3A4 inducers with Larotrectinib. If coadministration of a strong CYP3A4 inducer cannot be avoided, double the Larotrectinib dose. After the inducer has been discontinued for 3 to 5 elimination half-lives, resume the Larotrectinib dose taken prior to initiating the CYP3A4 inducer.

Dosage Modifications for Patients with Hepatic Impairment

Reduce the starting dose of Larotrectinib by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment.

CONTRAINDICATION

None

WARNING AND 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 modifica tion included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).

Advise patients and caretakers of these risks with Larotrectinib. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue Larotrectinib based on the severity. If withheld, modify the Larotrectinib dosage 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.

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue Larotrectinib based on the severity. If withheld, modify the Larotrectinib dosage 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. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively , those observed at the clinical dose of 100 mg twice daily. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of Larotrectinib.

SIDE EFFECTS

Neurotoxicity: [see Warnings and Precautions]

Hepatotoxicity: [see Warnings and Precautions]

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. Avoid coadministration of Larotrectinib with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If coadministration of strong CYP3A4 inhibitors cannot be avoided, modify Larotrectinib dose as recommended.

Strong CYP3A4 Inducers

Coadministration of Larotrectinib with a strong CYP3A4 inducer may decrease Larotrectinib plasma concentrations, which may decrease the efficacy of Larotrectinib. Avoid coadministration of Larotrectinib with strong CYP3A4 inducers, including St. John's wort. If coadministration of strong CYP3A4 inducers cannot be avoided, modify Larotrectinib dose as recommended.

Effects of Larotrectinib 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. Avoid coadministration of Larotrectinib with sensitive CYP3A4 substrates.

If coadministration of these sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs

USE IN SPECIFIC POPULATION

Pregnancy

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 embryo-fetal harm when administered to a pregnant woman. There are no available data on Larotrectinib use in pregnant women.

Lactation

There is 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, advise women not to breastfeed during treatment with Larotrectinib and for 1 week after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating Larotrectinib.

Contraception

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

Females

Advise female patients of reproductive potential to use effective contraception during treatment with Larotrectinib and for at least 1 week after the final dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with Larotrectinib and for 1 week after the final dose.

Pediatric Use

Due to the small number of pediatric and adult patients, the single arm design of clinical studies of Larotrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to Larotrectinib are related to patient age or other factors. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients compared to adult patients were increased weight (11% vs. 2%) and neutropenia (20% vs. 2%). One of the 44 pediatric patients discontinued Larotrectinib due to an adverse reaction (Grade 3 increased ALT).

The pharmacokinetics of Larotrectinib in the pediatric population were similar to those seen in adults.

Geriatric Use

Of 176 patients in the overall safety population who received Larotrectinib, 22% of patients were ≤0 65 years of age and 5% of patient s were ≤0 75 years of age. Clinical studies of Larotrectinib did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A). Larotrectinib clearance was reduced in subjects with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. Reduce Larotrectinib dose as recommended.

Renal Impairment

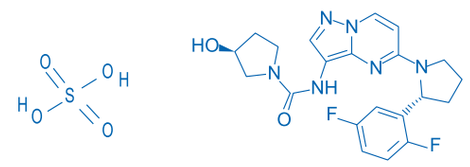
No dose adjustment is recommended for patients with renal impairm ent of any severity.

OVERDOSE

No information available.

DESCRIPTION

Larotrectinib is a kinase inhibitor. The molecular formula for Larotr ectinib sulfate is $C_{21}H_{24}F_2N_6O_6S$ and the molecular weight is 526.51 g/mol for the sulfate salt and 428.44 g/mol for the free base. The chemical name is (3S)-N-{5-[(2R)-2-(2,5-difluoro phenyl)-1-pyrrolidinyl] pyrazolo [1,5-a] pyrimidin-3-yl}-3-hy droxy-1-pyrrolidinecarboxamide sulfate. Larotrectinib sulfate has the following chemical structure:



Larotrectinib sulfate is an off-white to pinkish yellow solid that is not hygroscopic. The aqueous solubility of larotrectinib at 37°C is pH dependent (very soluble at pH 1.0 and freely soluble at pH 6.8, according to USP descriptive terms of solubility).

CLINICAL 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 ICso 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-fram e fusions of these genes with various partners can result in constitutively-activated chimeric TRK fusion proteins that can act as an oncogenic driver, promoting cell proliferation and survival in tumor cell lines.

In in vitro and in vivo tumor models, Larotrectinib demonstrated anti-tumor activity in cells with constitutive activation of TRK p roteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression. Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to Larotrectinib include G623R, G696A, and F617L.

NON CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with Larotrectinib. Larotrectinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assays, with or without metabolic activation, or in the in vitro mammalian mutagenesis assays, with or without metabolic activation. In vivo, Larotrectinib was negative in the mouse micronucleus test.

Fertility studies with Larotrectinib have not been conducted. In a 3-month repeat-dose toxicity study in the rat, Larotrectinib had no effects on spermatogenes is at 75 mg/kg/day (approximately 7 times the human exposure at the 100 mg twice daily dose). Additionally, Larotrect inib had no histological effects on the male reproductive tract in rats or monkeys at doses resulting in exposures up to 1O times the human exposure ($AUC_{0\text{-}24hr}$) at the 100 mg twice daily clinical dose.

In a 1-month repeat-dose study in the rat, decreased uterine weight and uterine atrophy were seen at 200 mg/kg/day [approximately 45 times the human exposure (AUC) at the 100 mg twice daily dose]. Fewer corpora lutea and increased incidence of anestrus were also noted at doses ≥60 mg/kg/day (approximately 10 times the human exposure at the 100 mg twice daily dose). Decreased fertility occurred in a juvenile animal study. There were no findings in female reproductive organs in repeat-dose studies in monkeys at exposures up to 22 times the human exposure at the 100 mg twice daily dose.

PHARMACEUTICAL INFORMATION

Storage

Store below 30°C. Keep out of the sight & reach of children. Protect from moisture & light.

Packing

Larogen 25 Capsule: Each HDPE container contains 30 capsules and one packet silica gel in a sealed plastic container.

Larogen 100 Capsule: Each HDPE container contains 30 capsules and one packet silica gel in a sealed plastic container.

Manufactured by:

general GENERAL Pharmaceuticals Ltd.
Mouchak, Kaliakair, Gazipur, Bangladesh
www.generalpharma.com

22066353-V00

The information given here is limited. For further information consult your doctor or pharmacist.