Larotrectinib (Systemic)

Antineoplastic agent; a potent and selective inhibitor of tropomyosin receptor kinase (Trk) A, TrkB, and TrkC.

Class: 10:00 • Antineoplastic Agents (AHFS primary)

Brands: Vitrakvi®

Uses

Solid Tumors with Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion

- Treatment of solid tumors harboring an *NTRK* fusion (without a known acquired mutation for resistance) in patients who have metastatic disease or may experience severe morbidity following surgical resection and whose disease progressed following prior therapy or those who are not candidates for other treatment options (designated an orphan drug by FDA for these cancers).
- Accelerated approval based on overall response rate and duration of response. Continued approval may be contingent on verification and description of clinical benefit in confirmatory studies.
- Confirmation of the presence of *NTRK* fusion is necessary prior to initiation of therapy. In clinical studies, *NTRK* fusion status of tumor specimens was determined by fluorescence in situ hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), or next-generation sequencing (NGS).

Dosage and Administration

General

- Confirm presence of *NTRK* fusion prior to initiation of therapy. (See Solid Tumors with Neurotrophic Receptor Tyrosine Kinase [*NTRK*] Gene Fusion under Uses.)

Restricted Distribution

- Obtain larotrectinib only through designated specialty pharmacies and distributors.
- Contact the manufacturer at 844-634-8725 or consult the Vitrakvi® website (https://www.vitrakvi.com) for specific ordering and availability information.

Administration

Oral Administration

Capsules

Administer orally twice daily without regard to meals.

Swallow capsules whole with a full glass of water; do not chew or crush.

Oral Solution

Administer orally twice daily without regard to meals.

Use an oral dosing syringe; follow the patient instructions provided by the manufacturer.

Dosage

Available as larotrectinib sulfate; dosage expressed in terms of larotrectinib.

Oral solution and capsules may be interchanged at equal doses.

Pediatric Patients

Solid Tumors with *NTRK* Fusion

Oral: Body surface area (BSA) <1 m^2: 100 mg/m^2 twice daily.

BSA ≥1 m^2: 100 mg twice daily.

Continue therapy until disease progression or unacceptable toxicity occurs.

If concomitant use with potent CYP3A4 inhibitors or inducers cannot be avoided, adjust dosage of larotrectinib. (See Interactions.)

Dosage Modification for Toxicity

If grade 3 or 4 adverse reaction occurs, interrupt therapy for up to 4 weeks. If resolution or improvement to grade 1 or baseline observed within 4 weeks, resume drug at reduced dosage (or discontinue) as described in Table 1. Permanently discontinue therapy if grade 3 or 4 adverse reaction does not improve within 4 weeks of treatment interruption.

Table 1. Dosage Modifications for Larotrectinib Toxicity in Pediatric Patients.

Toxicity Occurrence	Pediatric Patients with BSA ≥1 m^2 (Starting Dosage = 100 mg twice daily)	Pediatric Patients with BSA <1 m^2 (Starting Dosage = 100 mg/m^2 twice daily)
First	Restart at 75 mg twice daily	Restart at 75 mg/m^2 twice daily
Second	Restart at 50 mg twice daily	Restart at 50 mg/m^2 twice daily
Third	Restart at 100 mg once daily	Restart at 25 mg/m^2 twice daily
Fourth	Permanently discontinue drug	Permanently discontinue drug

Adults

Solid Tumors with *NTRK* Fusion

Oral: 100 mg twice daily. Continue therapy until disease progression or unacceptable toxicity occurs.

If concomitant use with potent CYP3A4 inhibitors or inducers cannot be avoided, adjust dosage of larotrectinib. (See Interactions.)

Dosage Modification for Toxicity

If grade 3 or 4 adverse reaction occurs, interrupt therapy for up to 4 weeks. If resolution or improvement to grade 1 or baseline observed within 4 weeks, resume drug at reduced dosage (or discontinue) as described in Table 2. Permanently discontinue therapy if grade 3 or 4 adverse reaction does not improve within 4 weeks of treatment interruption.

Oral:

Table 2. Dosage Modifications for Larotrectinib Toxicity in Adults.

Toxicity Occurrence	Dosage Modification after Recovery from Toxicity (Starting Dosage = 100 mg twice daily)
First	Restart at 75 mg twice daily
Second	Restart at 50 mg twice daily
Third	Restart at 100 mg once daily
Fourth	Permanently discontinue drug

Special Populations

Hepatic Impairment

Moderate or severe hepatic impairment (Child-Pugh class B or C): Reduce initial dosage by 50% (e.g., dosage of 100 mg twice daily reduced to 50 mg twice daily; dosage of 100 mg/m^2 twice daily reduced to 50 mg/m^2 twice daily). (See Hepatic Impairment under Cautions.)

Mild hepatic impairment (Child-Pugh class A): No dosage adjustment required.

Renal Impairment

No dosage adjustment required. (See Renal Impairment under Cautions.)

Geriatric Patients

No specific dosage recommendations. (See Geriatric Use under Cautions.)

Cautions

Contraindications

- Manufacturer states none known.

Warnings/Precautions

Neurologic Effects

Adverse neurologic effects (i.e., delirium, dysarthria, dizziness, gait disturbances, paresthesia, memory impairment, tremor) and grade 4 encephalopathy reported. Generally occurs within 3 months of initiation of therapy, but may occur as early as 1 day or as late as 2.2 years following initiation of therapy.

If neurologic events occur, therapy interruption followed by dosage reduction or permanent discontinuance of drug may be necessary. (See Dosage Modification for Toxicity under Dosage and Administration: Pediatric Patients and Dosage and Administration: Adults, and also see Advice to Patients.)

Hepatotoxicity

ALT or AST elevations reported. Median time to occurrence 2 months (range: 1 month to 2.6 years).

Monitor liver function tests, including ALT and AST concentrations, every 2 weeks for the first month of therapy and then monthly thereafter or more frequently as clinically indicated.

If hepatotoxicity occurs, therapy interruption followed by dosage reduction or permanent discontinuance of drug may be necessary. (See Dosage Modification for Toxicity under Dosage and Administration: Pediatric Patients and Dosage and Administration: Adults.)

Fetal/Neonatal Morbidity and Mortality

Based on its mechanism of action and animal findings, larotrectinib may cause fetal harm. Embryofetal toxicity and teratogenicity demonstrated in animals. Crosses placenta in animals.

Possible association between decreased Trk-mediated signaling and obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis based on data from individuals with congenital mutations in the Trk pathway.

Perform pregnancy test prior to initiating larotrectinib therapy in women of reproductive potential. Avoid pregnancy during therapy and for ≥1 week after drug discontinuance. Advise women of reproductive potential and men who are partners of such women to use effective contraception while receiving the drug and for ≥1 week after discontinuance of therapy. If used during pregnancy or if patient becomes pregnant, apprise patient of potential fetal hazard.

Impairment of Fertility

Results of animal studies suggest larotrectinib may impair female fertility.

Specific Populations

Pregnancy

May cause fetal harm. (See Fetal/Neonatal Morbidity and Mortality under Cautions.)

Lactation

Not known whether larotrectinib distributes into milk, affects milk production, or affects nursing infants.

Women should not breast-feed during therapy and for 1 week following drug discontinuance.

Pediatric Use

Safety and efficacy not established in pediatric patients <28 days of age. Efficacy of larotrectinib for solid tumors harboring *NTRK* fusion in pediatric patients is supported by 3 noncomparative studies that included 12 patients ≥28 days of age. Based on limited safety data in 44 pediatric patients receiving the drug, grade 3 or 4 weight gain or neutropenia occurred more frequently in pediatric patients compared with adults.

No differences in pharmacokinetics observed between pediatric patients and adults.

Geriatric Use

In clinical trials evaluating larotrectinib, 22% of patients were ≥65 years of age and 5% were ≥75 years of age. Insufficient experience in patients ≥65 years of age to determine whether they respond differently than younger patients.

Hepatic Impairment

Systemic exposure increased in individuals with moderate or severe hepatic impairment (Child-Pugh class B or C); dosage adjustment is necessary. (See Special Populations under Pharmacokinetics and also see Hepatic Impairment under Dosage and Administration.)

Systemic exposure not substantially altered in individuals with mild hepatic impairment (Child-Pugh class A).

Renal Impairment

Systemic exposure not substantially altered in individuals with end-stage renal disease requiring dialysis. (See Special Populations under Pharmacokinetics.)

Common Adverse Effects

Fatigue, nausea, dizziness, cough, vomiting, constipation, diarrhea, dyspnea, pyrexia, peripheral edema, weight gain, myalgia/arthralgia, headache, abdominal pain, decreased appetite, muscular weakness, back or extremity pain, hypertension, fall, nasal congestion, elevated ALT and/or AST concentrations, anemia, hypoalbuminemia, elevated alkaline phosphatase concentrations, neutropenia.

Interactions

Metabolized principally by CYP3A4.

Inhibits CYP3A4 in vitro. Does not inhibit or induce CYP isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations in vitro.

Substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT2, organic anion transport protein (OATP) 1B1, and OATP1B3 in vitro. Does not inhibit P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, bile salt export pump (BSEP), multidrug and toxin extrusion (MATE) transporter 1, and MATE2K at clinically relevant concentrations in vitro.

Drugs and Foods Affecting Hepatic Microsomal Enzymes

Potent inhibitors of CYP3A4: Potential pharmacokinetic interaction (increased systemic exposure to larotrectinib) and increased risk of toxicity. Avoid concomitant use. If concomitant use cannot be avoided, reduce larotrectinib dosage by 50% (e.g., dosage of 100 mg twice daily reduced to 50 mg twice daily; dosage of 100 mg/m^2 twice daily reduced to 50 mg/m^2 twice daily). When concomitant use of the potent CYP3A4 inhibitor is discontinued, return larotrectinib dosage (after 3–5 elimination half-lives of the CYP3A4 inhibitor) to dosage used prior to initiation of the potent CYP3A4 inhibitor. (See Specific Drugs and Foods under Interactions.)

Potent inducers of CYP3A4: Potential pharmacokinetic interaction (decreased systemic exposure to larotrectinib) and reduced larotrectinib efficacy. Avoid concomitant use. If concomitant use cannot be avoided, double dosage of larotrectinib (e.g., dosage of 100 mg twice daily increased to 200 mg twice daily; dosage of 100 mg/m^2 twice daily increased to 200 mg/m^2 twice daily). When concomitant use of the potent CYP3A4 inducer is discontinued, return larotrectinib dosage (after 3–5 elimination half-lives of the CYP3A4 inducer) to dosage used prior to initiation of the potent CYP3A4 inducer. (See Specific Drugs and Foods under Interactions.)

Drugs Metabolized by Hepatic Microsomal Enzymes

Substrates of CYP3A4: Potential pharmacokinetic interaction (increased systemic exposure to CYP3A4 substrate) and increased adverse effects. Avoid concomitant use with sensitive CYP3A4 substrates. If concomitant use cannot be avoided, monitor for CYP3A4 substrate-related toxicity. (See Specific Drugs and Foods under Interactions.)

Specific Drugs and Foods

Drug or Food	Interaction	Comments
Grapefruit or grapefruit juice	Potential increased systemic exposure to larotrectinib and increased risk of toxicity	Avoid concomitant use
Itraconazole	Increased peak plasma concentrations and AUC of larotrectinib by 2.8- and 4.3-fold, respectively	Avoid concomitant use; if concomitant use cannot be avoided, reduce larotrectinib dosage by 50% When itraconazole is discontinued, return larotrectinib dosage (after 3–5 elimination half-lives of itraconazole) to prior dosage
Midazolam	Potential increased peak plasma concentrations and AUC of midazolam (a CYP3A4 substrate) and increased toxicity	Avoid concomitant use; if concomitant use cannot be avoided, monitor for midazolam toxicity
Rifampin	Multiple-dose rifampin (potent CYP3A inducer) decreased peak plasma concentration and AUC of larotrectinib by 71 and 81%, respectively Single-dose rifampin (P-gp inhibitor) increased peak plasma concentration and AUC of larotrectinib by 1.8- and 1.7-fold	Avoid concomitant use; if concomitant use cannot be avoided, double dosage of larotrectinib When rifampin is discontinued, return larotrectinib dosage (after 3–5 elimination half-lives of rifampin) to prior dosage
St. John's wort *(Hypericum perforatum)*	Potential decreased peak plasma concentrations and AUC of larotrectinib and reduced efficacy	Avoid concomitant use; if concomitant use cannot be avoided, double dosage of larotrectinib When St. John's wort is discontinued, return larotrectinib dosage (after 3–5 elimination half-lives of St. John's wort) to prior dosage

Pharmacokinetics

Absorption

Bioavailability

Systemic exposure increases in a dose-proportional manner over a dose range of 100–400 mg and in a slightly more than dose-proportional manner over a dose range of 600–900 mg.

Peak plasma concentrations achieved in approximately 1 hour following oral administration of larotrectinib capsules.

Steady-state concentrations are achieved within 3 days.

Mean absolute oral bioavailability is 34% following oral administration of larotrectinib capsules.

AUC of oral solution similar to that observed with larotrectinib capsules; however, peak plasma concentrations are 36% higher following administration of the oral solution.

Food

Administration with a high-fat meal decreased peak plasma concentrations by 35% and delayed time to peak plasma concentrations by 2 hours, but did not substantially affect the extent of absorption.

Special Populations

Mild or moderate hepatic impairment (Child-Pugh class A or B): AUC increased by 1.3- or 2-fold, respectively; peak plasma concentrations similar to those in individuals with normal hepatic function.

Severe hepatic impairment (Child-Pugh class C): AUC and peak plasma concentrations increased by 3.2- and 1.5-fold, respectively.

End-stage renal disease requiring dialysis: AUC and peak plasma concentrations increased by 1.5- and 1.3-fold, respectively.

Moderate or severe renal impairment (Cl_{cr} ≤60 mL/minute): Pharmacokinetics not studied.

Age (28 days to 82 years), sex, or body weight (3.8–179 kg) does not affect pharmacokinetics of larotrectinib.

Distribution

Extent

Crosses placenta in animals.

Not known whether larotrectinib is distributed into milk.

Plasma Protein Binding

70% (independent of larotrectinib concentration).

Elimination

Metabolism

Principally metabolized by CYP3A4.

Elimination Route

Eliminated in feces (58% [5% as unchanged drug]) and urine (39% [20% as unchanged drug]).

Half-life

2.9 hours.

Stability

Storage

Oral

Capsules

20–25°C (may be exposed to 15–30°C).

Solution

2–8°C. Do not freeze.

Opened bottles: 2–8°C. Discard after 90 days of first opening.

Actions

- Potent and selective inhibitor of TrkA, TrkB, and TrkC.
- TrkA, TrkB, and TrkC are encoded by *NTRK1*, *NTRK2*, and *NTRK3* and are involved in the initiation of various cascades of intracellular signaling events (i.e., Ras/MAPK/ERK, PI3K/Akt, and PLCγ1/Pkc signal transduction pathways) that lead to cell proliferation, differentiation, apoptosis, and regulation of processes critical to neuron survival in the central and peripheral nervous systems.
- Chromosomal rearrangements of *NTRK1*, *NTRK2*, and *NTRK3* genes result in formation of a constitutively active chimeric Trk oncogenic fusion protein and dysregulation of Trk signaling and subsequent tumorigenesis.
- Inhibits wild-type TrkA, TrkB, and TrkC.
- Induces antitumor activity in cell lines with Trk expression from constitutive activation, deletion of a protein regulatory domain, or overexpression of wild-type Trk.
- Inhibits tyrosine kinase nonreceptor 2 (TNK2).
- Clinical resistance attributed to secondary point mutations of the NTRK kinase domain in 90% of cases. Demonstrates minimal activity in cell lines with point mutations in the TrkA kinase domain, including the acquired resistance mutation G595R. Acquired resistance also identified in cells lines with G623R, G696A, and F617L point mutations in the TrkC kinase domain.

Advice to Patients

- Importance of instructing patients to read the manufacturer's patient information.
- Importance of advising patients to take larotrectinib exactly as prescribed and to not alter the dosage or discontinue therapy unless advised to do so by their clinician. Importance of advising patients to swallow larotrectinib capsules whole and to not chew or crush the capsules.
- Importance of advising patients to take a missed dose as soon as it is remembered unless the dose was missed by more than 6 hours, in which case they should not take the missed dose. If a dose is vomited, importance of administering the next dose at the regularly scheduled time.
- Risk of adverse neurologic effects. Importance of informing clinician if new or worsening manifestations of neurologic events (e.g., confusion; speech difficulties; dizziness; coordination difficulties; tingling, numbness, or burning sensation in hands and feet) occur. Necessity of advising patients to avoid driving or operating hazardous machinery if they experience neurologic events.
- Risk of hepatotoxicity; importance of regular liver function test monitoring. Importance of immediately informing clinician if signs or symptoms of hepatotoxicity (e.g., loss of appetite, nausea, vomiting, abdominal pain [especially right upper quadrant pain]) occur.
- Risk of fetal harm. Necessity of advising women of reproductive potential to avoid pregnancy and to use effective contraceptive methods while receiving larotrectinib and for ≥1 week following discontinuance of therapy. Importance of advising men who are partners of such women that they should use effective methods of contraception while receiving the drug and for ≥1 week after the drug is discontinued. Importance of women informing their clinicians if they become pregnant during therapy or think they may be pregnant. Advise men and women of reproductive potential of potential risk to the fetus.
- Importance of advising women to avoid breast-feeding while receiving larotrectinib and for 1 week after discontinuance of therapy.
- Risk of impaired female fertility.
- Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and dietary or herbal supplements (e.g., St. John's wort [*Hypericum perforatum*], grapefruit, grapefruit juice), as well as any concomitant illnesses (e.g., hepatic impairment).
- Importance of informing patients of other important precautionary information. (See Cautions.)

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Distribution of larotrectinib is restricted. (See Restricted Distribution under Dosage and Administration.)

Larotrectinib Sulfate

Oral

Capsules		
	25 mg (of larotrectinib)	**Vitrakvi®**, Loxo Oncology
	100 mg (of larotrectinib)	**Vitrakvi®**, Loxo Oncology
Solution		
	20 mg (of larotrectinib) per mL	**Vitrakvi®**, Loxo Oncology