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

<table>
<thead>
<tr>
<th>Toxicty Occurrence</th>
<th>Pediatric Patients with BSA ≥1 m² (Starting Dosage = 100 mg twice daily)</th>
<th>Pediatric Patients with BSA &lt;1 m² (Starting Dosage = 100 mg/m² twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Restart at 75 mg twice daily</td>
<td>Restart at 75 mg/m² twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>Restart at 50 mg twice daily</td>
<td>Restart at 50 mg/m² twice daily</td>
</tr>
<tr>
<td>Third</td>
<td>Restart at 100 mg once daily</td>
<td>Restart at 25 mg/m² twice daily</td>
</tr>
<tr>
<td>Fourth</td>
<td>Permanently discontinue drug</td>
<td>Permanently discontinue drug</td>
</tr>
</tbody>
</table>

**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.**

<table>
<thead>
<tr>
<th>Toxicity Occurrence</th>
<th>Dosage Modification after Recovery from Toxicity (Starting Dosage = 100 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Restart at 75 mg twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>Restart at 50 mg twice daily</td>
</tr>
<tr>
<td>Third</td>
<td>Restart at 100 mg once daily</td>
</tr>
<tr>
<td>Fourth</td>
<td>Permanently discontinue drug</td>
</tr>
</tbody>
</table>

**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/m² twice daily reduced to 50 mg/m² 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 discontinuation 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 discontinuation 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**

**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.vitraki.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.

**Pediatric Patients**

<table>
<thead>
<tr>
<th>Solid Tumors with NTRK Fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral: Body surface area (BSA) &lt;1 m²: 100 mg/m² twice daily. BSA ≥1 m²: 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.)</td>
</tr>
</tbody>
</table>

**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.

**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®

AHFS DI® Essentials 2019 • Page 1 of 3
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 2 weeks after drug discontinuation. Advise women of reproductive potential and men who are partners of such women to use effective contraception while receiving the drug and for 2 weeks 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/arthritis, headache, abdominal pain, decreased appetite, muscular weakness, back or extremity pain, hypertension, fall, nasal congestion, elevated ALT and/or AST concentrations, anemia, hypoaalbuminemia, elevated alkaline phosphatase concentrations, neutropenia.

### 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

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

When St. John’s wort is discontinued, return larotrectinib dosage (after 3–5 eliminating 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 (CrCl ≤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**
- 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**
- Importance of instructing 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.
- 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 fatal 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**
Exciipients 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

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