Larotrectinib Sulfate

10:00 • Antineoplastic Agents (AHFS primary)

■ Larotrectinib, a potent and selective inhibitor of tropomyosin receptor kinase (Trk) A, TrkB, and TrkC, is an antineoplastic agent.

Uses

■ Solid Tumors with Neurotrophic Receptor Tyrosine Kinase Gene Fusion

Larotrectinib sulfate is used for the treatment of solid tumors harboring a neurotrophic receptor tyrosine kinase (*NTRK*) gene 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. The presence of *NTRK* fusion should be confirmed prior to initiation of therapy. An FDA-approved diagnostic test for detection of *NTRK* fusion is not currently available; however, in clinical studies, presence of *NTRK* fusion was determined by fluorescence in situ hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), or next-generation sequencing (NGS). Larotrectinib has been designated an orphan drug by FDA for the treatment of these cancers. The accelerated approval of larotrectinib for this indication is based on overall response rate and duration of response. Continued approval for this indication may be contingent on verification and description of clinical benefit of larotrectinib in confirmatory studies.

The incidence of solid tumors harboring activating *NTRK* fusions has not been fully characterized; however, 1500–5000 cases are estimated per year in the US. Although a relatively small subset (less than 1%) of patients with common solid tumors (e.g., lung, colon, or prostate cancer) harbor *NTRK* fusions, such fusions have been frequently reported in certain rare cancers (i.e., 91–100% of mammary analogue secretory carcinomas, secretory breast carcinomas, or infantile fibrosarcomas; 61% of congenital mesoblastic nephromas; 12–15% of papillary thyroid cancers).

The current indication for larotrectinib in the treatment of solid tumors harboring *NTRK* fusion is based principally on data from 3 open-label noncomparative studies (LOXO-TRK-14001, SCOUT, and NAVIGATE) evaluating larotrectinib in patients with unresectable or metastatic solid tumors harboring *NTRK* fusion. The primary efficacy population consisted of the initial 55 adult and pediatric patients enrolled in the LOXO-TRK-14001, SCOUT, and NAVIGATE studies with solid tumors harboring an *NTRK* fusion. Patients were eligible for these studies if they experienced disease progression following prior systemic therapy, if available, or if severe morbidity following surgical resection for locally advanced disease was expected. In these studies, adult patients received larotrectinib 100 mg orally twice daily and pediatric patients (18 years of age or younger) received larotrectinib 100 mg/m^2 (maximum dose of 100 mg) orally twice daily. Therapy was continued until the occurrence of unacceptable toxicity or disease progression. The primary efficacy end points were overall response rate and duration of response (as evaluated by a blinded independent review committee) according to Response Evaluation Criteria in Solid Tumors (RECIST). In the primary efficacy population, the median age of patients was 45 years (range: 4 months to 76 years); 78% of patients were 18 years of age or older, 22% were younger than 18 years of age, 93% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 67% were white, 7% were Hispanic or Latino, 4% were Asian, and 4% were black. Most patients (82%) had metastatic disease and 18% had unresectable locally advanced disease. The majority (98%) of patients in the primary efficacy population had received prior surgery, radiation therapy, or systemic therapy for their disease; 82% of these patients had received a median of 2 prior systemic therapies and 35% had received at least 3 prior systemic therapies. The most common cancers in the primary efficacy population were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%).

At the time of data analysis, the overall response rate in the primary efficacy population was 75%; complete response was achieved in 22% of patients. The median duration of response had not been reached at the time of the analysis; however, 73, 63, or 39% of patients had durable responses of 6, 9, or 12 months or longer, respectively. The overall response rate in patients with infantile fibrosarcoma, thyroid carcinoma, gastrointestinal stromal tumor (GIST), soft tissue sarcoma, salivary gland cancer, lung cancer, melanoma, or colon cancer was 100, 100, 100, 91, 83, 75, 50, or 25%, respectively. Stable disease was reported in patients with cholangiocarcinoma, appendix cancer, or pancreatic cancer while progressive disease was reported in one patient with breast cancer. The most common *NTRK* fusion was *ETV6-NTRK3*; however, *NTRK* fusions were inferred in 3 patients with infantile fibrosarcoma with documented *ETV6* translocation as detected by FISH. The overall response rate in patients with tumors harboring inferred *ETV6-NTRK3*, *IRF2BP2-NTRK1*, *SQSTM1-NTRK1*, documented *ETV6-NTRK3*, *TPM3-NTRK1*, or *LMNA-NTRK1* fusion was 100, 100, 100, 84, 56, or 40%, respectively. Although *PDE4DIP-NTRK1*, *PPL-NTRK1*, *STRN-NTRK2*, *TPM4-NTRK3*, *TPR-NTRK1*, and *TRIM63-NTRK1* fusions were detected in one patient each, patients with tumors harboring these *NTRK* fusions achieved complete or partial responses.

Dosage and Administration

■ General

Presence of a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion must be confirmed prior to initiation of therapy with larotrectinib. (See Uses: Solid Tumors with Neurotrophic Receptor Tyrosine Kinase Gene Fusion.)

Restricted Distribution

Larotrectinib sulfate can only be obtained through designated specialty pharmacies and distributors. Clinicians may contact the manufacturer (Bayer) at 844-634-8725 or consult the Vitrakvi® website (https://www.vitrakvi.com) for specific ordering and availability information.

■ Administration

Larotrectinib is administered orally (as capsules or oral solution) twice daily without regard to meals. The capsules should be swallowed whole with water; they should *not* be chewed or crushed. The oral solution should be administered using an oral dosing syringe according to the manufacturer's directions.

Larotrectinib capsules should be stored at room temperature of 20–25ºC, but may be exposed to 15–30ºC.

Larotrectinib oral solution should be stored in a refrigerator at 2–8ºC; the oral solution should not be frozen. Unused portions of larotrectinib oral solution should be discarded after 90 days of opening the bottle.

■ Dosage

Dosage of larotrectinib sulfate is expressed in terms of larotrectinib.

The oral solution and capsules may be interchanged at equal doses.

Solid Tumors with Neurotrophic Receptor Tyrosine Kinase Gene Fusion

For the treatment of solid tumors harboring *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, the recommended dosage of larotrectinib in *adult and pediatric patients with a body surface area (BSA) of at least 1 m^2* is 100 mg twice daily. In *pediatric patients with a BSA less than 1 m^2*, the recommended dosage of larotrectinib is 100 mg/m^2 twice daily.

Larotrectinib therapy should be continued until disease progression or unacceptable toxicity occurs.

Dosage Modification for Toxicity

If a grade 3 or 4 adverse reaction occurs, larotrectinib therapy should be withheld. If the grade 3 or 4 adverse reaction resolves to grade 1 or baseline within 4 weeks of withholding larotrectinib, the drug should be resumed at a reduced dosage (or discontinued) as described in Table 1. If the grade 3 or 4 adverse reaction does not resolve within 4 weeks of withholding larotrectinib, the drug should be permanently discontinued.

Table 1. Dosage Modifications for Larotrectinib Toxicity.

	Dosage Modification after Recovery from Toxicity	
Toxicity Occurrence	Adult and Pediatric Patients with BSA of 1 m^2 or More (Starting Dosage = 100 mg twice daily)	Pediatric Patients with BSA Less than 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 larotrectinib	Permanently discontinue larotrectinib

Concomitant Use with CYP3A4 Inhibitors or Inducers

Concomitant use of larotrectinib with *potent inhibitors of cytochrome P-450 (CYP) isoenzyme 3A4* should be avoided; however, if such concomitant use cannot be avoided, the manufacturer recommends reducing the dosage of larotrectinib 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, the larotrectinib dosage should be returned (after at least 3–5 elimination half-lives of the CYP3A4 inhibitor) to the dosage used prior

to initiation of the potent CYP3A4 inhibitor. (See Inhibitors of CYP3A4 under Drug Interactions: Drugs and Foods Affecting Hepatic Microsomal Enzymes.)

Concomitant use of larotrectinib with *potent inducers of CYP3A4* should be avoided; however, if such concomitant use cannot be avoided, the manufacturer recommends doubling the 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, the larotrectinib dosage should be returned (after at least 3–5 elimination half-lives of the CYP3A4 inducer) to the dosage used prior to initiation of the potent CYP3A4 inducer. (See Inducers of CYP3A4 under Drug Interactions: Drugs and Foods Affecting Hepatic Microsomal Enzymes.)

■ Special Populations

For patients with moderate or severe hepatic impairment (Child-Pugh class B or C), the manufacturer recommends reducing the initial dosage of larotrectinib 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). No initial dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). (See Hepatic Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

The manufacturer states that no adjustment to the dosage of larotrectinib is necessary in patients with renal impairment. (See Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

The manufacturer makes no specific dosage recommendations for geriatric patients. (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Cautions

■ Contraindications

The manufacturer states that there are no known contraindications to the use of larotrectinib sulfate.

■ Warnings/Precautions

Neurologic Effects

Larotrectinib can cause a variety of adverse neurologic effects including delirium, dysarthria, dizziness, gait disturbance, paresthesia, memory impairment, and tremor. In the principal efficacy studies of larotrectinib in patients with unresectable or metastatic solid tumors, neurologic events occurred in 53% of 176 patients receiving the drug and were grade 3 or 4 in 6 or 0.6%, respectively, of patients. Most patients (65%) experienced neurologic events within 3 months of initiation of larotrectinib therapy; however, neurologic events have occurred as early as 1 day or as late as 2.2 years following initiation of the drug. Grade 4 encephalopathy also was reported in 1 of 176 patients (0.6%) receiving larotrectinib. Temporary interruption or dosage reduction of larotrectinib was necessary because of dizziness, gait disturbance, delirium, memory impairment, or tremor in 3, 1, 1, 1, or 1%, respectively, of patients receiving the drug.

Temporary interruption of larotrectinib therapy followed by dosage reduction or permanent discontinuance of therapy may be necessary in patients experiencing neurologic events during therapy with the drug, and such patients should be advised not to drive or operate machinery. (See Dosage Modification for Toxicity under Dosage and Administration: Dosage.)

Hepatotoxicity

Elevations in aminotransferase (ALT and/or AST) concentrations have been reported in patients receiving larotrectinib. In the principal efficacy studies of larotrectinib in patients with unresectable or metastatic solid tumors, elevations in serum concentrations of ALT or AST occurred in 45% of 176 patients receiving the drug and were grade 3 or 4 in 6 or 0.6%, respectively, of patients. The median time to occurrence of elevated ALT or AST concentration was 2 months (range: 1 month to 2.6 years). Temporary interruption or dosage reduction of larotrectinib was necessary because of elevated AST or ALT concentrations in 4 or 6%, respectively, of patients receiving the drug. Therapy was discontinued because of elevations in ALT or AST concentrations in 2% of patients receiving the drug.

Liver function tests, including ALT and AST concentrations, should be monitored every 2 weeks for the first month of therapy and then monthly thereafter or more frequently as clinically indicated. Temporary interruption of larotrectinib therapy followed by dosage reduction or permanent discontinuance of therapy may be necessary if hepatotoxicity occurs. (See Dosage Modification for Toxicity under Dosage and Administration: Dosage.)

Fetal/Neonatal Morbidity and Mortality

Larotrectinib may cause fetal harm in humans based on its mechanism of action and animal findings; embryofetal toxicity and teratogenicity have been demonstrated in animals. There are no available data regarding use of larotrectinib in pregnant women. Larotrectinib has been shown to cross the placenta in animals. In animal reproduction studies, fetal anasarca and omphalocele were observed in rats and rabbits receiving larotrectinib at exposure levels approximately 11 and 0.7 times the human exposure, respectively, at the recommended dosage. Literature reports in individuals with congenital mutations in the tropomyosin receptor kinase (Trk) pathway suggest an association between decreased Trk-mediated signaling and obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

Pregnancy should be avoided during larotrectinib therapy. The manufacturer recommends confirmation of pregnancy status prior to initiation of larotrectinib in women of reproductive potential and states that such women should be advised to use effective contraceptive methods while receiving larotrectinib and for at least 1 week after discontinuance of the drug. In addition, men with such female partners should use effective methods of contraception while receiving larotrectinib and for at least 1 week after discontinuance of the drug. Patients should be apprised of the potential hazard to the fetus if larotrectinib is used during pregnancy.

Impairment of Fertility

Based on animal studies, larotrectinib may impair female fertility. The effect of the drug on fertility in humans is not known. In a repeat-dose toxicity study, decreased uterine weight, uterine atrophy, decreased corpora lutea, and increased incidence of anestrus were observed in female rats receiving larotrectinib at exposure levels approximately 10–45 times the human exposure at the recommended dosage.

Specific Populations

Pregnancy.

Larotrectinib may cause fetal harm if administered to pregnant women based on its mechanism of action and animal findings. (See Fetal/Neonatal Morbidity and Mortality under Cautions: Warnings/Precautions.)

Lactation.

It is not known whether larotrectinib or its metabolites are distributed into human milk. Because of the potential for serious adverse reactions to larotrectinib in breast-fed infants, women should be advised not to breast-feed while receiving the drug and for 1 week after the last dose. The effects of the drug on breast-fed infants or on the production of milk are unknown.

Pediatric Use.

Safety and efficacy of larotrectinib have not been established in pediatric patients younger than 28 days. Efficacy of larotrectinib in pediatric patients with solid tumors harboring a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion has been established in 3 noncomparative studies that included 12 pediatric patients 28 days of age or older. Based on limited safety data in 44 pediatric patients receiving larotrectinib, some grade 3 or 4 adverse effects and laboratory abnormalities (i.e., weight gain, neutropenia) occurred more frequently in pediatric patients compared with adults; however, because the studies were uncontrolled, it is unclear whether this effect was related to larotrectinib or to other confounding factors (e.g., differences in susceptibility to infection). No differences in pharmacokinetics were observed between pediatric patients and adults.

Geriatric Use.

In clinical trials evaluating larotrectinib in patients with unresectable or metastatic solid tumors, 22% of patients receiving larotrectinib were 65 years of age or older, while 5% were 75 years of age or older. There is insufficient experience in patients 65 years of age or older to determine whether geriatric patients respond differently than younger patients.

Hepatic Impairment.

Following administration of a single 100-mg dose of larotrectinib, the area under the plasma concentration-time curve (AUC) in individuals with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C) was increased by 1.3-, 2-, or 3.2-fold, respectively, compared with individuals with normal hepatic function; peak plasma concentrations were increased by 1.5-fold in individuals with severe hepatic impairment compared with individuals with normal hepatic function. Initial dosage adjustment is required in patients with moderate or severe hepatic impairment. (See Dosage and Administration: Special Populations.)

Renal Impairment.

Following administration of a single 100-mg dose of larotrectinib to individuals with end-stage renal disease requiring dialysis, AUC and peak plasma concentrations were increased by 1.5- and 1.3-fold, respectively, compared with individuals with normal renal function (creatinine clearance of 90 mL/minute or greater). Larotrectinib has not been studied in patients with moderate or severe renal impairment (creatinine clearance of 60 mL/minute or less).

■ Common Adverse Effects

Adverse effects reported in at least 10% of patients receiving larotrectinib include 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, and nasal congestion. Laboratory abnormalities reported in at least 5% of patients receiving larotrectinib include elevated concentrations of aminotransferases (i.e., ALT, AST), anemia, hypoalbuminemia, elevated concentrations of alkaline phosphatase, and neutropenia.

Drug Interactions

Larotrectinib is metabolized principally by cytochrome P-450 (CYP) isoenzyme 3A4.

In vitro studies indicate that larotrectinib is an inhibitor of CYP3A4. In vitro, larotrectinib does not inhibit or induce CYP isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations.

In vitro, larotrectinib is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate for organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT2, organic anion transport protein (OATP) 1B1, or OATP1B3. In vitro studies indicate that larotrectinib 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.

■ Drugs and Foods Affecting Hepatic Microsomal Enzymes

Inhibitors of CYP3A4

Concomitant use of larotrectinib with potent inhibitors of CYP3A4 may increase systemic exposure to larotrectinib and possible toxicity. When the potent CYP3A inhibitor itraconazole (200 mg once daily for 7 days) was administered concomitantly with larotrectinib (single 100-mg dose), peak plasma concentration and area under the plasma concentration-time curve (AUC) of larotrectinib were increased by 2.8- and 4.3-fold, respectively. The potential for moderate or weak CYP3A inhibitors to alter larotrectinib pharmacokinetics has not been established.

Concomitant use of larotrectinib with potent inhibitors of CYP3A4 (e.g., itraconazole, grapefruit juice) should be avoided. If concomitant use of a potent CYP3A4 inhibitor cannot be avoided, the manufacturer recommends reducing the dosage of larotrectinib 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, the larotrectinib dosage should be returned (after at least 3–5 elimination half-lives of the CYP3A4 inhibitor) to the dosage used prior to initiation of the potent CYP3A4 inhibitor.

Inducers of CYP3A4

Concomitant use of larotrectinib with potent inducers of CYP3A4 may decrease systemic exposure to larotrectinib and reduce larotrectinib efficacy. When the potent CYP3A inducer rifampin (600 mg once daily for 11 days) was administered concomitantly with larotrectinib (single 100-mg dose), peak plasma concentration and AUC of larotrectinib were decreased by 71 and 81%, respectively. The potential for moderate or weak CYP3A inducers to alter larotrectinib pharmacokinetics has not been established.

Concomitant use of larotrectinib with potent inducers of CYP3A4 (e.g., rifampin, St. John's wort [*Hypericum perforatum*]) should be avoided. If concomitant use of a potent CYP3A4 inducer cannot be avoided, the manufacturer recommends doubling the 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, the larotrectinib dosage should be returned (after at least 3–5 elimination half-lives of the CYP3A4 inducer) to the dosage used prior to initiation of the potent CYP3A4 inducer.

■ Drugs Metabolized by Hepatic Microsomal Enzymes

Substrates of CYP3A4

Larotrectinib may increase systemic exposure and risk of adverse effects of other drugs metabolized by CYP3A4. When the sensitive CYP3A4 substrate midazolam (single 2-mg dose) was administered concomitantly with larotrectinib (100 mg twice daily for 10 days) in healthy individuals, peak plasma concentration and AUC of midazolam were both increased by 1.7-fold; peak plasma concentration and AUC of the major metabolite of midazolam (1-hydroxymidazolam) were both increased by 1.4-fold. Concomitant use with sensitive substrates of CYP3A4 (e.g., midazolam) should be avoided. If concomitant use of a sensitive CYP3A4 substrate cannot be avoided, the patient should be monitored for CYP3A4 substrate-related toxicity.

■ Drugs Affecting the P-glycoprotein Transport System

When the P-gp inhibitor rifampin (single 600-mg dose) was administered concomitantly with larotrectinib (single 100-mg dose) in healthy individuals, peak plasma concentration and AUC of larotrectinib were increased by 1.8- and 1.7-fold, respectively. (See Drug Interactions: Drugs and Foods Affecting Hepatic Microsomal Enzymes.)

Description

Larotrectinib, a potent and selective inhibitor of tropomyosin receptor kinase (Trk) A, TrkB, and TrkC, is an antineoplastic agent. The Trk family of tyrosine kinases (encoded by the neurotrophic receptor tyrosine kinase genes *NTRK1*, *NTRK2*, and *NTRK3*) 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), which leads to cell proliferation, differentiation, apoptosis, and regulation of processes critical to neuron survival in the central and peripheral nervous systems. Chromosomal rearrangements of the *NTRK1*, *NTRK2*, and *NTRK3* genes result in fusions with an unrelated gene. These *NTRK* gene fusions encode a constitutively active chimeric Trk oncogenic fusion protein resulting in dysregulation of Trk signaling and subsequent tumorigenesis. In vitro biochemical assays have shown that larotrectinib inhibits the activity of wild-type TrkA, TrkB, and TrkC. In vitro and in vivo, larotrectinib has demonstrated antitumor activity in cell lines with Trk expression from constitutive activation, deletion of a protein regulatory domain, or overexpression of wild-type Trk. Larotrectinib also has demonstrated inhibition of tyrosine kinase nonreceptor 2 (TNK2).

Clinical resistance to larotrectinib has been attributed to secondary point mutations of the NTRK kinase domain in 90% of cases. Larotrectinib has shown minimal activity in cell lines with point mutations in the TrkA kinase domain, including the acquired resistance mutation G595R. Acquired resistance to larotrectinib also has been identified in cell lines with G623R, G696A, or F617L point mutations in the TrkC kinase domain.

Following oral administration of larotrectinib capsules, systemic exposure to larotrectinib increases in a dose-proportional manner over a dose range of 100–400 mg and increases in a slightly more than dose-proportional manner over a dose range of 600–900 mg. Following oral administration of larotrectinib capsules at a dosage of 100 mg twice daily, peak plasma concentrations of the drug were achieved in approximately 1 hour and steady-state concentrations were achieved within 3 days. The mean absolute oral bioavailability of larotrectinib capsules was 34%. The area under the plasma-concentration time curve (AUC) for larotrectinib oral solution was similar to the AUC for larotrectinib capsules; peak plasma concentrations were 36% higher for larotrectinib oral solution compared with larotrectinib capsules. Administration of larotrectinib capsules (single 100-mg dose) with a high-fat meal decreased peak plasma concentrations by 35% and delayed the time to peak plasma concentrations by 2 hours compared with administration in the fasted state, but did not substantially affect the extent of absorption. Larotrectinib is metabolized principally by cytochrome P-450 (CYP) isoenzyme 3A4. Larotrectinib is 70% bound to plasma proteins, and binding is independent of larotrectinib concentration. Following oral administration of a single 100-mg radiolabeled dose of larotrectinib, 58% of the dose was recovered in feces (5% as unchanged drug) and 39% was recovered in urine (20% as unchanged drug). The terminal half-life of larotrectinib is 2.9 hours.

The pharmacokinetics of larotrectinib do not appear to be affected by age (range of 28 days to 82 years), sex, or body weight (range of 3.8–179 kg).

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 at least 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 at least 1 week after the drug is discontinued. Importance of women informing 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.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity. For further information on the handling of antineoplastic

agents, see the ASHP Guidelines on Handling Hazardous Drugs at http://www.ahfsdruginformation.com.

Preparations

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

Larotrectinib sulfate can only be obtained through designated specialty pharmacies and distributors. (See Restricted Distribution under Dosage and Administration: General.)

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