Drug Monograph

A - Drug Name

larotrectinib

COMMON TRADE NAME(S): Vitrakvi®

back to top

B - Mechanism of Action and Pharmacokinetics

Larotrectinib is a tropomyosin receptor kinase (TRK) inhibitor, which targets the TRK proteins including TRKA, TRKB, and TRKC that are encoded by the NTRK1, NTRK2 and NTRK3 genes respectively. Gene fusion events of NTRK1, NTRK2 and NTRK3 lead to oncogenic TRK fusion proteins formation. These proteins can cause constitutive kinase activity, activating downstream cell signalling pathways involved in cell growth and survival.

Absorption	Larotrectinib capsule or oral solution have equivalent oral bioavailability. AUC was similar following larotrectinib oral solution administration compared to the capsule; Cmax was 36% higher with the oral solution.	
	Bioavailability	34% (mean)
	Effects with food	After a high-fat and high-calorie meal, there was a 35% reduction in C_{max} with no effect on AUC compared to overnight fasting.
	T max	~1 hour (mean)
	Time to reach steady state	within 8 days
Distribution	PPB	70%
	Cross blood brain barrier?	Low (in animal studies)

Metabolism	Active metabolites	Unknown
	Inactive metabolites	Yes
Elimination	Feces	58% (5% unchanged)
	Urine	39% (20% unchanged)
	Half-life	~3 hours (mean)

back to top

C - Indications and Status

Health Canada Approvals:

- Solid tumours (Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion-positive)

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

back to top

D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following adverse events were reported in ≥ 10% of adult and pediatric patients treated with at least one dose of larotrectinib in a pooled analysis of Phase 1 or 2 studies.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Rash (10%)	E
Gastrointestinal	Abdominal pain (13%)	E
	Anorexia (13%)	E
	Constipation (27%)	E
	Diarrhea (25%)	E
	Nausea, vomiting (28%)	E

	Weight gain (16%)	E
General	Edema - limbs (15%)	E
	Fatigue (26%)	E
Hematological	Myelosuppression ± infection, bleeding (28%) (including anemia) (8% severe)	E
Hepatobiliary	↓ albumin (11%)	E
	↑ LFTs (30%) (4% severe)	E D
Musculoskeletal	Fracture (7%)	E D L
	Musculoskeletal pain (18%)	E
Nervous System	Cognitive disturbance (11%) (may be severe)	E D
	Dizziness (22%)	E D
	Headache (16%)	E D
	Mood changes (14%) (neurologic/psychiatric) (may be severe)	E D
	Peripheral neuropathy (5%)	E
	Sleep disorder (11%)	E D
Renal	Creatinine increased (11%)	E
Respiratory	Cough, dyspnea (27%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for larotrectinib include ↑ LFTs, myelosuppression ± infection, bleeding, nausea, vomiting, constipation, cough, dyspnea, fatigue, diarrhea, dizziness, musculoskeletal pain and weight gain.

Increased LFTs have been reported and may be severe. Cases of hepatotoxicity including drug-induced liver injury (DILI) have been reported.

Skeletal fractures can occur in patients taking larotrectinib with a median onset of 13 months. Most fractures were associated with minimal or moderate trauma.

Neurologic/psychiatric events occurred in 61% of patients, including Grade ≥ 3 events in ~12% of patients. The majority (72%) of neurologic events occurred within three months of treatment initiation. Grade 5 depressed level of consciousness and cerebellar hemorrhage were reported in one patient each.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Confirm the presence of NTRK gene fusion in a tumour specimen using a validated test prior to initiation.

Adults:

Larotrectinib capsule or oral solution have equivalent oral bioavailability.

Oral: 100 mg BID

Refer to interactions section for dosing recommendations when co-administered with **CYP3A inducers** or **inhibitors**.

Dosage with Toxicity:

Dose Level	Larotrectinib Dose
0	100 mg twice daily
-1	75 mg twice daily
-2	50 mg twice daily
-3	100 mg **once** daily
-4	Discontinue

Toxicity	Severity	Action
Hepatic toxicity	Grade 2 ALT and/or AST (> 3 to 5 x ULN)	Monitor liver function closely until resolved, to establish whether a dose interruption or reduction is required.
	Grade 3 ALT and/or AST (> 5 to 20 x ULN), with bilirubin < 2 x ULN	Hold until ≤ Grade 1 or baseline; monitor liver function closely. Restart only if the benefit outweighs the risk at 1 dose level ↓. Discontinue if it does not resolve or if a Grade 4 ALT and/or AST elevation occurs after restarting treatment.
	Grade 4 ALT and/or AST (> 20 x ULN), with bilirubin < 2 x ULN	
	ALT and/or AST ≥ 3 x ULN, with bilirubin ≥ 2 x ULN	Hold until ≤ Grade 1 or baseline; monitor liver function closely. Consider discontinuation. Restart only if the benefit outweighs the risk at 1 dose level ↓ with close monitoring. Discontinue if recurs.
Other toxicities	Grade 3 or 4	Hold up to 4 weeks until ≤ Grade 1 or baseline; restart at 1 dose level ↓. Discontinue if it does not resolve after 4 weeks.

Dosage with Hepatic Impairment:

Hepatic Impairment	Starting Dose (% of usual dose)
Child-Pugh A	No dose adjustment
Child-Pugh B or Child-Pugh C	50%

Dosage with Renal Impairment:

No dose adjustment is required for patients with renal impairment.

Dosage in the elderly:

No dose adjustment is necessary in elderly patients. Age has no effect on the systemic exposure of larotrectinib. The safety profile in patients ≥ 65 years was generally consistent with younger patients. Adverse effects that were observed more frequently in elderly patients included fatigue, anemia, dizziness, fall, gait disturbance, hyponatremia, dyspnea, anorexia, muscular weakness and peripheral neuropathy.

Dosage based on gender:

Gender had no significant effect on the exposure of larotrectinib.

Dosage based on ethnicity:

Ethnicity had no significant effect on the exposure of larotrectinib.

Children:

Safety and efficacy have been established in pediatric patients ≥ 28 days of age. There are no data in pediatric patients < 1 month of age. Severe neutropenia occurred more frequently in pediatric patients compared to adults.

Refer to dosing information in the product monograph.

back to top

F - Administration Guidelines

- Administer larotrectinib with or without food.
- Capsules should be swallowed whole with a glass of water and not crushed, dissolved, or opened.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during larotrectinib treatment.
- If a dose is missed, the dose should be skipped and the next dose should be taken at the usual time. Patients should not take two doses at the same time to make up for a missed dose.
- If the patient vomits after taking a dose, an additional dose should not be taken.
- Store capsules at room temperature 15°C to 30°C.
- Store oral solution refrigerated at 2°C to 8°C. Do not freeze. Discard 30 days after first opening.

back to top

G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any of its components

Other Warnings/Precautions:

- Patients should use caution when driving, operating machinery or performing tasks that require alertness if they experience fatigue or neurologic adverse events while taking larotrectinib.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: No
- Embryotoxicity: Not demonstrated in animal studies
- Teratogenicity: Documented in animals
- Crosses placental barrier: Documented in animals
- Pregnancy:
  Larotrectinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 month** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **1 week** after the last dose.
- Fertility effects:
  Documented in studies with female animals.

back to top

H - Interactions

Larotrectinib is a substrate of cytochrome CYP3A, P-gp and BCRP.

In vitro, larotrectinib is not a substrate for the transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, or OATP1B3.

In vitro, larotrectinib induces CYP2B6 and is a weak inhibitor of CYP3A4/5.

Co-administration with strong P-gp inducers or inhibitors may affect larotrectinib plasma concentrations.

Larotrectinib is unlikely to be affected by pH-modifying agents.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inhibitors (e.g. atazanavir, clarithromycin, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, voriconazole, grapefruit or grapefruit juice)	↑ larotrectinib exposure (↑ Cmax by 2.8-fold and ↑ AUC by 4.3-fold with itraconazole)	↓ metabolism of larotrectinib	Avoid concomitant use; if unavoidable, reduce larotrectinib dose by 50%. If the CYP3A inhibitor is discontinued, increase the larotrectinib dose (after 3-5 half-lives of the inhibitor) to the dose used before starting the inhibitor.
Moderate CYP3A4 inhibitors (i.e. fluconazole or diltiazem)	↑ larotrectinib exposure (↑ Cmax by 1.9-fold and ↑ AUC by 2.7-fold)	↓ metabolism of larotrectinib	Monitor for toxicity; reduce larotrectinib dose as clinically indicated.
Strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, or St John's Wort)	↓ larotrectinib exposure (↓ Cmax by 71% and ↓ AUC by 81% with rifampin)	↑ metabolism of larotrectinib	Avoid concomitant use; if unavoidable, double larotrectinib dose. If the CYP3A4 inducer is discontinued, decrease the larotrectinib dose (after 3-5 half-lives of the inducer) to the dose used before starting the inducer.
Moderate CYP3A4 inducers (i.e. efavirenz)	↓ larotrectinib exposure (↓ Cmax by 60% and ↓ AUC by 72%)	↑ metabolism of larotrectinib	Double larotrectinib dose. If the CYP3A4 inducer is discontinued, decrease the larotrectinib dose (after 3-5 half-lives of the inducer) to the dose used before starting the inducer.
CYP3A4 substrates (e.g. midazolam, fentanyl, cyclosporine, dihydroergotamine, pimozide, quinidine,	↑ substrate exposure (↑ Cmax and AUC of midazolam by 1.7-fold)	Larotrectinib is a CYP3A4 inhibitor	Avoid concomitant use of substrates with narrow therapeutic range; if unavoidable, monitor for toxicity and consider dose reduction of substrate.

sirolimus, or tacrolimus).

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline, every 2 weeks for the first month, then monthly for the next 6 months, and at each visit (more frequent in patients who develop transaminase elevations)
CBC	Baseline and at each visit
Renal function tests	Baseline and as clinically indicated
Clinical toxicity assessment for infection, bleeding, fatigue, weight gain, GI, neurological and psychiatric effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- larotrectinib - For the treatment of unresectable locally advanced, or metastatic solid tumours with neurotrophic tyrosine receptor kinase (NTRK) gene fusion, according to clinical criteria

back to top

K - References

BC Cancer. BC Cancer Protocol Summary for the Treatment of Solid Tumours with Neurotrophic Tyrosine Receptor Kinase (NTRK) Fusion using Larotrectinib. Sept 2023.

European Medicines Agency. Assessment Report: Vitrakvi. July 2019.

Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. J Clin Oncol. 2020 Aug 20;38(24):2782-2797.

Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020 Apr;21(4):531-40.

Hong DS, Shen L, van Tilburg CM, et al. Long-term efficacy and safety of larotrectinib in an integrated dataset of patients with TRK fusion cancer. J Clin Oncol 2021 39:15 suppl, 3108.

Prescribing Information: Vitrakvi® (larotrectinib). Bayer HealthCare Pharmaceuticals Inc. April 2025..

Product Monograph: Vitrakvi® (larotrectinib). Bayer Inc. September 3, 2024.

September 2025 New drug monograph

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top