DRUG NAME: Larotrectinib

SYNONYM(S): LOXO-101[1]

COMMON TRADE NAME(S): VITRAKVI®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Larotrectinib is an orally administered, potent and highly selective inhibitor of Tropomyosin Receptor Kinase (TRK). Larotrectinib targets TRKA, TRKB, and TRKC which are receptor tyrosine kinases encoded by the Neurotrophic Tyrosine Receptor Kinase (NTRK) genes NTRK1, NTRK2, and NTRK3, respectively. Chromosomal rearrangements of the NTRK genes lead to the formation of TRK fusion proteins which act as oncogenic drivers that promote cell proliferation and survival of tumour cell lines. By inhibiting the TRK proteins, larotrectinib inhibits proliferation of cell lines containing NTRK gene fusions in a concentration-dependent manner, and significantly inhibits tumour growth.[1-4]

PHARMACOKINETICS:

Oral Absorption	bioavailability = 34%; C_{max} is 36% higher with oral solution vs capsule; high-fat, high-calorie meal decreases C_{max} by 35%, but has no effect on AUC	
Distribution	blood to plasma concentration ratio = 0.9	
	cross blood brain barrier?	poor brain distribution[5]
	volume of distribution	48 L
	plasma protein binding	70% (independent of drug concentration)
Metabolism	primarily metabolized by CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	O-linked glucuronide metabolite
Excretion	urinary and fecal elimination	
	urine	39% (20% unchanged)
	feces	58% (5% unchanged)
	terminal half life	2.9 h
	clearance	98 L/h
Sex	no clinically significant difference	
Elderly	similar C_{max} and AUC in patients >65 years compared to patients <65 years	
Children	age 1 month to <3 months: 3-fold higher exposure compared to age ≥18 years; age ≥3 months to 12 years: higher C_{max} but similar AUC compared to ≥18 years; >12 years: similar C_{max} and AUC compared to ≥18 years	
Body weight	larotrectinib AUC may be increased in children weighing <5 kg	
Ethnicity	no clinically significant difference	

Adapted from standard reference[1,2,4,5] unless specified otherwise.

Developed: 1 July 2022
Revised: 1 September 2023

USES:

Primary uses:

*Solid tumours, NTRK gene fusion-positive

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***ability to drive or operate machinery*** may be compromised as neurologic adverse events and fatigue are common[2,4]
- patients with pre-existing ***hepatic impairment*** may require starting dose reduction[2,4]
- co-administration with ***strong CYP 3A4 inhibitors or inducers*** may require dose modification[2,4]

Special populations:

- ***pediatric patients*** experience a higher incidence of grade 3 or 4 neutropenia (9-20% vs 0-2%) and weight gain (2-11% vs 0-2%) compared to adult patients[2]
- ***patients aged 65 years and older*** experience fatigue, anemia, dizziness, fall, gait disturbance, and hyponatremia more frequently than younger patients[2]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Larotrectinib is not clastogenic in mammalian *in vivo* chromosome test.[2,4]

Fertility: In animal studies, female test subjects had fewer corpora lutea, the incidence of anestrus was increased, and uterine weights were decreased (with uterine atrophy) at exposures 8 times higher than those seen following human clinical exposure. These effects were reversible. No effects on spermatogenesis or the histopathology of male reproductive organs were observed at exposures 7-10 times higher than those seen following human clinical exposure.[2,4]

Pregnancy: In animal studies, larotrectinib was shown to cross the placenta in more than one species and was detected in fetal blood samples. Larotrectinib was not embryotoxic at exposures up to maternally toxic doses. However, when dosed during organogenesis, malformations including omphalocele and anasarca were observed at maternal exposures 0.6-9 times higher than those seen following human clinical exposure. For females of childbearing potential, a pregnancy test is recommended prior to starting treatment. Contraception is advised during treatment and for at least one month after the last dose in female patients of childbearing potential and in male patients with female partners of childbearing potential.[2,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for one week following the last dose.[2,4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[6,7]. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group. **Incidence data in the Side Effect table includes both pediatric and adult patients.**

Developed: 1 July 2022
Revised: 1 September 2023

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (25-42%, severe 9-10%)
	leukopenia (11-28%, severe <2%)
	lymphopenia (13-22%, severe 4-6%)
	neutropenia (13-36% severe 7-14%)
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain (14-21%, severe 2%)
	constipation (27%, severe <1%)
	diarrhea (26-27%, severe 1%)
	nausea (25%, severe 1%)
	vomiting (25%, severe 1%)
general disorders and administration site conditions	***edema, peripheral*** (16-19%, severe <1%)
	fatigue (33-36%, severe 3%)
	pyrexia (23-24%, severe 2%)
infections and infestations	***pneumonia*** (severe 3%)
	sepsis (severe 1%)
	upper respiratory infection (13%)
	urinary tract infection (11-12%, severe 1%)
injury, poisoning, and procedural complications	***skeletal fractures*** (7-9%); median time to fracture 11.6 months (most fractures are associated with minimal or moderate trauma)
investigations	alkaline phosphatase increase (34%, severe 2%)
	ALT increase (28-45%, severe 3%); median time to onset 1.8 months
	AST increase (25-52%, severe 3%); median time to onset 1.5 months
	creatinine increase (10%, severe 1%)
	hypocalcemia (25%, severe 3%)
	weight increase (14%, severe 4%)
metabolism and nutrition	appetite decrease (12%, severe 1%)
	hypoalbuminemia (10-36%, severe 1-2%)
	hypoglycemia (severe 1%)
	hypokalemia (severe 3%)
	hypophosphatemia (severe 3%)
	hyponatremia (severe 1%)
musculoskeletal and connective tissue	arthralgia (16%, severe 1%)
	back pain (13%, severe 1%)
	muscle weakness (10%, severe 1%)
	musculoskeletal pain (42%, severe 4%)

Developed: 1 July 2022
Revised: 1 September 2023

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	myalgia (17%, severe 1%)
	pain in extremity (14%, severe 1%)
nervous system see paragraph following **Side Effects** table	brain edema (severe <1%)
	cerebrovascular accident (severe <1%)
	cognitive impairment (11%, severe 3%)
	dizziness (26-27%, severe 1%)
	dysgeusia (6%)
	encephalopathy (severe <1%)
	gait disturbance (6%, severe 1%)
	headache (15%, severe <1%)
	mental status change (severe 1%)
	paresthesia (6%, severe 1%)
	peripheral neuropathy (5%)
	seizure (severe <1%)
	syncope (severe 1%)
psychiatric see paragraph following **Side Effects** table	***mood disorders*** (14%, severe <1%)
	sleep disorders (10%)
respiratory, thoracic and mediastinal	***cough*** (30-32%, severe <1%)
	dyspnea (17%, severe 3%)
	nasal congestion (11%)
skin and subcutaneous tissue	***rash*** (19%, severe <1%)

Adapted from standard reference[1,2,4] unless specified otherwise.

The safety profile of larotrectinib in the ***pediatric*** population is generally consistent with that of the adult population. Most adverse events are grade 1 or 2 and resolve without dose modification or treatment discontinuation. Some adverse events are reported with higher frequency in pediatric patients than in adults (e.g., neutropenia, thrombocytopenia, leukopenia, transaminase elevations, vomiting, diarrhea, fractures, and upper respiratory tract infections).[2,4]

Neurologic/psychiatric adverse events are reported in up to 63% of patients and include dizziness, cognitive impairment, mood disorders, and sleep disorders. The majority of events occur within the first three to six months of treatment. Patients should not drive or operate potentially hazardous machinery if they are experiencing neurologic symptoms. Cognitive impairment has a median time to onset of 5 to 6 months and may include memory impairment, confusion, disturbance in attention, and delirium. Mood disorders have a median time to onset of ~4 months and may include anxiety, depression, agitation, and irritability. Sleep disorders may include insomnia, somnolence, and other sleep disturbances. Based on the severity of the symptoms, larotrectinib dose interruption, dose reduction, or treatment discontinuation may be required.[2,4]

Developed: 1 July 2022
Revised: 1 September 2023

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[2,4]	may increase plasma level of larotrectinib	may inhibit CYP 3A4 metabolism of larotrectinib in the intestinal wall	avoid grapefruit juice for 48 hours before and for duration of larotrectinib therapy
itraconazole[2,4]	2.8-fold increase in C_{max} and 4.3-fold increase in AUC of larotrectinib	strong CYP 3A4 inhibition by itraconazole	avoid concurrent use; if unavoidable, reduce larotrectinib dose by 50%
midazolam[2,4]	1.7-fold increase in C_{max} and AUC of midazolam	inhibition of CYP 3A4 by larotrectinib	avoid concurrent use; if unavoidable, monitor for midazolam toxicity
pH-modifying agents[2]	*in vitro* studies show that larotrectinib is fully soluble over the entire pH range of the gastrointestinal tract	pH-dependent solubility of larotrectinib	none required
rifampin[2,4]	71% decrease in C_{max} and 81% decrease in AUC of larotrectinib	strong CYP 3A4 induction by rifampin	avoid concurrent use; if unavoidable, increase larotrectinib dose to double the dose and monitor for toxicity

Larotrectinib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentration of larotrectinib. Avoid concurrent use with strong CYP 3A4 inhibitors. If coadministration cannot be avoided, larotrectinib dose reduction by 50% is required. If the CYP 3A4 inhibitor is discontinued, larotrectinib may be resumed at its prior dose following a washout period equal to 3 to 5 elimination half-lives of the inhibitor.[2,4]

CYP 3A4 ***inducers*** may decrease the plasma concentration of larotrectinib. Avoid concurrent use with strong CYP 3A4 inducers. If coadministration cannot be avoided, the larotrectinib dose may be doubled. If the CYP 3A4 inducer is discontinued, larotrectinib may be resumed at its prior dose following a washout period equal to 3 to 5 elimination half-lives of the inducer.[2,4]

Larotrectinib is a metabolism-dependent irreversible inhibitor of CYP 3A4 *in vitro*, which contributes to a weak inhibition effect clinically. During coadministration with a CYP 3A4 substrate with a narrow therapeutic index, monitor for toxicity of the substrate. Dose modification of the substrate may be required.[2,4]

Larotrectinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Inhibitors or inducers of P-gp and BRCP may respectively increase or decrease the plasma concentration of larotrectinib; clinical significance is unknown.[2]

Larotrectinib is an inducer of CYP 2B6 *in vitro*; clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral:
Bayer Inc. supplies larotrectinib as 25 mg and 100 mg hard gelatin capsules. Store at room temperature.[9]

Bayer Inc. supplies larotrectinib as a 20 mg/mL oral solution (2 x 50 mL bottles in each carton). Solution is clear yellow to orange/red/brown colour, and has a strawberry flavour. Solution contains propylene glycol and sodium benzoate. Refrigerate. Discard 30 days after first opening.[9]

Additional information:
- oral solution and capsule may be used interchangeably[9]

Developed: 1 July 2022
Revised: 1 September 2023

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:[9-11]	***100 mg*** (range 50-100 mg) ***PO twice daily**** (NOTE: once daily dosing may be required for some recommended dose modifications) *dose adjustment may be required for some drug interactions Oral solution and capsule may be used interchangeably. Administer with food or on an empty stomach. Do not take with grapefruit or grapefruit juice.
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:[2,4]	no adjustment required
Dosage in hepatic failure:[2,4]	mild-impairment (Child-Pugh A): no adjustment required moderate/severe impairment (Child-Pugh B/C): decrease starting dose by 50%
Dosage in dialysis:	no information found

Children:	safety and efficacy in children <1 month of age have not been established[2,4]; sodium benzoate (excipient in oral solution) may increase jaundice in newborn babies up to 4 weeks old[9]
Oral:[2,4]	In children ≥1 month of age: 100 mg/m^2 (range 25-100 mg/m^2) PO* twice daily maximum = 100 mg per dose *oral solution can be administered by mouth or enterally via naso- or gastric-feeding tube Rounding volume for oral solution: volumes <1.0 mL can be rounded to the nearest 0.1 mL volumes >1.0 mL can be rounded to the nearest 0.5 mL
Dosage in myelosuppression:	modify according to protocol by which patient is being treated

Developed: 1 July 2022
Revised: 1 September 2023

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Developed: 1 July 2022
Revised: 1 September 2023