PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrVITRAKVI®

larotrectinib capsules
25 mg and 100 mg larotrectinib (as larotrectinib sulfate)

larotrectinib oral solution
20 mg/mL larotrectinib (as larotrectinib sulfate)

Antineoplastic Agent

(ATC: L01XE53)

VITRAKVI, indicated for:
- the treatment of adult and pediatric patients with solid tumours that:

- *have a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion without a known acquired resistance mutation,*
- *are metastatic or where surgical resection is likely to result in severe morbidity, and*
- *have no satisfactory treatment options*

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VITRAKVI please refer to Health Canada's Notice of Compliance with conditions - drug products web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php).

Bayer Inc.
2920 Matheson Blvd East,
Mississauga, Ontario
L4W 5R6
www.bayer.ca

Date of Initial Approval:
July 4, 2019

Date of Revision:
May 11, 2021

Submission Control No: 241249

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

TABLE OF CONTENTS

VITRAKVI, indicated for:
- the treatment of adult and pediatric patients with solid tumours that:

- *have a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion without a known acquired resistance mutation,*
- *are metastatic or where surgical resection is likely to result in severe morbidity, and*
- *have no satisfactory treatment options*

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VITRAKVI please refer to Health Canada's Notice of Compliance with conditions - drug products web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php).

PART I: HEALTH PROFESSIONAL INFORMATION

NOC/c

1. INDICATIONS

VITRAKVI (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumours that:

- have a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory treatment options.

This indication is approved based on overall response rate (ORR) and duration of response (DOR) in a pooled patient population in which most patients had rare tumours (see CLINICAL TRIALS).

Treatment with VITRAKVI should be initiated following confirmation of an *NTRK* gene fusion in a tumour specimen using a validated test (see ACTION AND CLINICAL PHARMACOLOGY - Mechanism of Action).

VITRAKVI should only be administered under the supervision of a health professional experienced in the use of antineoplastic agents.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of VITRAKVI in pediatric patients 28 days and older were established based upon data from three multicenter, open-label, single-arm clinical studies. There are no data in pediatric patients less than one month of age (see WARNINGS AND PRECAUTIONS: Special Populations - Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The safety and efficacy of VITRAKVI in geriatric patients were established based upon data from three multicenter, open-label, single-arm clinical studies. Insufficient numbers of patients aged 65 and over were included to determine whether they respond differently from younger subjects (see WARNINGS AND PRECAUTIONS: Special Populations - Geriatrics).

NOC/c

2. CONTRAINDICATIONS

VITRAKVI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

NOC/c

3. DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- Confirm the presence of an *NTRK* gene fusion in a tumour specimen using a validated test prior to initiation of treatment with VITRAKVI (see ACTION AND CLINICAL PHARMACOLOGY - Mechanism of Action).

3.2 Recommended Dose and Dosage Adjustment

Adults

The recommended dose of VITRAKVI in adults is 100 mg taken orally, twice daily (total dose of 200 mg) until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Pediatrics

Dosing in pediatric patients is based on body surface area (BSA). The recommended dose of VITRAKVI in pediatric patients (1 month to 18 years) is 100 mg/m^2 taken orally, twice daily with a maximum of 100 mg per dose (maximum total dose of 200 mg) until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. For those subjects following the BSA-based dosing algorithm (mg/m2), oral solution dose volumes under 1.0 mL can be rounded to the nearest 0.1 mL. Oral solution dose volumes above 1.0 mL can be rounded to the nearest 0.5 mL.

Geriatrics

Clinical data indicate that age has no effect on the systemic exposure of larotrectinib (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics - Special Populations and Conditions – Geriatrics:). No dose adjustment is necessary in elderly patients.

Patients with Hepatic Impairment

Clinical data from a pharmacokinetic study indicate that larotrectinib exposure was increased in patients with hepatic impairment up to 3.2-fold (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics - Special Populations and Conditions - Hepatic Insufficiency:). Reduce the starting dose of VITRAKVI by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild (Child-Pugh A) hepatic impairment.

Patients with Renal Impairment

Clinical data from a pharmacokinetic study indicate that larotrectinib exposure was increased 1.46-fold in patients with end-stage renal disease (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics - Special Populations and Conditions - Renal Insufficiency:). No dose adjustment is required for patients with renal impairment.

Dose Modifications

For an adverse reaction ≥ Grade 3, consider interrupting dosing of VITRAKVI and reevaluating regularly at least weekly. VITRAKVI can be withheld for up to 4 weeks to allow recovery to Grade 1 or back to baseline and resumed at the next dosage modification. Permanently discontinue VITRAKVI if an adverse reaction does not resolve within 4 weeks of the start of withholding the dose.

Recommended dose modifications for VITRAKVI for adverse reactions are provided in Table 1.

Table 1: Recommended Dose Modification for Adverse Reactions

Dose Modification	Adult and Pediatric Patients with Body Surface Area of at Least 1.0 m^2	Pediatric Patients with Body Surface Area Less Than 1.0 m^2
1st Dose Modification	75 mg orally twice daily	75 mg/m^2 orally twice daily
2nd Dose Modification	50 mg orally twice daily	50 mg/m^2 orally twice daily
3rd Dose Modification	100 mg orally once daily	25 mg/m^2 orally twice daily[a]

[a] *Pediatric patients on 25 mg/m^2 orally twice daily should remain on this dosage even if body surface area becomes greater than 1.0 m^2 during the treatment. Maximum dose should be 25 mg orally twice daily at the third dosage modification.*

Permanently discontinue VITRAKVI in patients who are unable to tolerate VITRAKVI after three dose modifications.

For all Grade 2 adverse reactions, continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised.

3.3 Administration

VITRAKVI is for oral use and may be administered with or without food. VITRAKVI is available as a capsule or oral solution formulation with equivalent oral bioavailability, and may be used interchangeably.

Capsule

The patient should be advised to swallow the capsule whole with water. The capsule should not be opened, chewed, or crushed.

Oral solution

Administer the oral solution by mouth or enterally by naso- or gastric- feeding tube with a dosing syringe.

3.4 Missed Dose

If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose. Patients should take the next dose at the next scheduled time.

If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting.

4. OVERDOSAGE

There is no known antidote for VITRAKVI. The treatment of overdose with VITRAKVI should consist of general supportive measures.

In clinical trials, the highest single dose of VITRAKVI was 900 mg, which is equivalent to 9-times a single recommended dose when taken twice daily. Among 12 healthy adult subjects who received a single dose of either 700 or 900 mg VITRAKVI, adverse events reported in ≥ 2 subjects consisted of nausea, vomiting, dizziness, and headache.

For management of a suspected drug overdose, contact your regional poison control centre.

5. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

VITRAKVI (larotrectinib) is supplied as white opaque hard gelatin capsules containing 25 mg and 100 mg of larotrectinib and as oral solution containing 20 mg/mL of larotrectinib.

Capsules

The 25 mg capsules are white opaque hard gelatin capsules (size 2) with blue printing of "BAYER" cross and "25 mg" on the body of capsule. They are supplied in 75 mL bottles of 56 capsules.

The 100 mg capsules are white opaque hard gelatin capsules (size 0) with blue printing of "BAYER" cross and "100 mg" on the body of capsule. They are supplied in 120 mL bottles of 56 capsules.

Oral Solution

The 20 mg/mL oral solution is clear yellow to orange liquid solution of citrus-berry flavor supplied in 100 mL amber glass bottle.

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	capsule 25 mg, 100 mg	Gelatin, printing ink (shellac, FD&C Blue # 2 aluminum lake, titanium dioxide, propylene glycol, ammonia solution, dimethicone), titanium dioxide
Oral	solution 20 mg/mL	Bitterness Masking Flavor (propylene glycol, natural flavour), Taste Modifier Flavor (propylene glycol, glycerol, natural flavour), hydroxypropyl betadex, Natural Bitterness Masking Type Flavor (glycerol, natural flavour ingredients), Natural Masking Type Flavor (glycerol, natural flavour ingredients), Ora-Sweet® (purified water, sucrose, glycerol, sorbitol, citric acid, sodium dihydrogen phosphate, flavouring and preservative agents methylparahydroxybenzoate and potassium sorbate), purified water, sodium citrate

NOC/c

6. WARNINGS AND PRECAUTIONS

Driving and Operating Machinery

Neurologic adverse events and fatigue have very commonly been reported in patients receiving VITRAKVI and may influence the patient's ability to drive and use machines. Caution patients and caretakers about driving and operating potentially hazardous machinery, until they are reasonably certain VITRAKVI therapy does not affect them adversely (see WARNINGS AND PRECAUTIONS - Neurologic).

Hepatic/Biliary/Pancreatic

Among the 279 patients who received VITRAKVI, treatment-emergent adverse events (TEAEs) of alanine transaminase (ALT) increased and aspartate transaminase (AST) increased of any grade were reported in 28% and 25% of patients, respectively. The maximum grades elevations were Grade 4 ALT increased in 2 patients (1%), Grade 4 AST increased in 1 patient (<1%), Grade 3 ALT increased in 7 patients (3%) and Grade 3 AST increased in 6 patients (2%)(see ADVERSE REACTIONS - Clinical Trial Adverse Reactions - Transaminase Elevations). The median time to onset of ALT increased was 1.8 months (range: 0 days to 21.3 months). The median time to onset of AST increased was 1.5 months (range: 0 days to 21.3 months). Transaminase elevations led to dose modification and permanent discontinuation of VITRAKVI in 3% and 2% of patients, respectively.

Monitor for liver function including ALT and AST assessments. VITRAKVI can cause transaminase elevations. Consider baseline assessment of liver function, including transaminase levels, before the first dose and monthly for the first 3 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase elevations. Withhold or permanently discontinue VITRAKVI based on the severity and persistence of the transaminase elevation. If withheld, modify the VITRAKVI dosage when resumed (see DOSAGE AND ADMINISTRATION, Dose Modifications). Patients with Grade 2 transaminase elevations should be followed with serial laboratory evaluations every one to two

weeks after the observation of Grade 2 toxicity to establish whether a dose interruption or reduction is required. In patients with ≥ Grade 3 events in whom VITRAKVI has been withheld, regular reevaluation at least weekly is recommended.

Neurologic/Psychiatric

Among the 279 patients who received VITRAKVI, neurologic/psychiatric TEAEs of any grade occurred in 63% of patients, including Grade 3 and Grade 4 adverse events in 11% and < 2% of patients, respectively. Grade 4 encephalopathy, brain edema, seizure and cerebrovascular accident were reported in one patient each. Grade 3 events included delirium (1%), dizziness (1%), mental status change (1%), gait disturbance (1%), paresthesia (1%), and syncope (1%). The majority (80%) of neurologic adverse events occurred within the first three months of treatment (range: 0 days to 35.5 months). Dose modification (interruption, increase or reduction) based on neurologic toxicity of all grades occurred in 11% of patients, most commonly for dizziness (2%) (see ADVERSE REACTIONS - Clinical Trial Adverse Reactions - Neurologic/Psychiatric events).

Withholding, reducing, or permanently discontinuing VITRAKVI dosing should be considered, depending on the severity and persistence of these symptoms.

Sexual Health

Reproduction

Based on the mechanism of action and non-clinical data, there may be a risk of fetal harm when administering larotrectinib to a pregnant woman. Females of childbearing potential should have a pregnancy test prior to starting treatment with VITRAKVI.

Advise female patients of reproductive potential to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose.

For males of reproductive potential with a non-pregnant female partner of child-bearing potential, advise use of highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose.

Fertility

There are no clinical data on the effect of VITRAKVI on fertility. Non-clinical fertility studies with larotrectinib have not been conducted; however, changes to the female reproductive organs in rats were observed in a repeated-dose toxicity study. Lower fertility was noted in juvenile rats at high dose (see NONCLINICAL TOXICOLOGY).

6.1 Special Populations

6.1.1 Pregnant Women

There are no clinical data on the use of VITRAKVI in pregnant women. In embryo-fetal development studies where pregnant rats and rabbits were dosed with larotrectinib during the period of organogenesis, malformations were observed at maternal exposures that were approximately 9- and 0.6- times, respectively, those observed at the clinical dose of 100 mg twice daily (see NONCLINICAL TOXICOLOGY). Larotrectinib crosses the placenta in animals.

Based on its mechanism of action and non-clinical data, there may be risk of fetal harm when larotrectinib is administered to a pregnant woman (see ACTION AND CLINICAL

PHARMACOLOGY - Mechanism of Action). Advise pregnant women of the potential risk to a fetus.

6.1.2 Breast-feeding

There are no data on the presence of larotrectinib in human milk, the effects of larotrectinib on the breastfed child, or the effects of larotrectinib on milk production. Because of the unknown risk of larotrectinib in nursing infants, advise a nursing woman to discontinue breastfeeding during treatment with VITRAKVI and for 1 week following the final dose.

6.1.3 Pediatrics

Among the 279 patients who received VITRAKVI, 92 (33%) were pediatric. Of these 92 patients, 36% were < 2 years (n=33), 41% were 2 years to < 12 years (n=38), and 23% were 12 years to < 18 years (n=21). The median duration of exposure was 7.4 months (range: 0.36 to 38.6 months). Treatment-emergent adverse events of Grade 3 or 4 severity occurring more frequently in pediatric patients compared to adult patients included increased weight (2% versus 0%) and neutropenia (9% versus 0%). Two pediatric patients discontinued VITRAKVI due to an adverse reaction Grade 3 ALT increased and neutrophil count decreased) (see ADVERSE REACTIONS - Clinical Trial Adverse Reactions (Pediatrics)).

Based on a population pharmacokinetic analysis, in pediatric patients from 1 to 3 months of age, the drug exposure was 3-fold higher than in adults when using recommended doses. The clinical relevance is unknown (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics).

6.1.4 Geriatrics

Among the 279 patients who received VITRAKVI, 54 (19%) patients were ≥ 65 years of age and 13 (5%) patients were ≥ 75 years of age. Clinical studies of VITRAKVI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see ADVERSE REACTIONS - Clinical Trial Adverse Reactions (Geriatrics).

NOC/c

7. ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The safety of VITRAKVI was evaluated in 279 patients. Overall, 99% of patients experienced at least one TEAE. The most commonly reported TEAEs (≥ 20%), in order of decreasing frequency, were fatigue, cough, ALT increased, constipation, diarrhea, dizziness, anemia, AST increased, vomiting nausea, and pyrexia.

The most common serious adverse events (≥ 2%) regardless of attribution included pneumonia, pyrexia, abdominal pain, diarrhea, and dyspnea.

Grade 3 or 4 TEAEs occurred in 53% of patients. Grade 4 events included sepsis, neutrophil count decreased, lymphocyte count decreased, ALT increased, hyponatremia, and hypoglycemia (1% for each). Grade 3 events included anemia (9%), weight increased (4%), hypophosphatemia (3%), fatigue (3%), ALT increased (3%), neutrophil count decreased (6%), dyspnea (3%), lymphocyte count decreased (4%), pneumonia (3%) and hypokalemia (3%).

Dose modification (interruption or reduction) of VITRAKVI dosage due to a TEAE occurred in 41% of patients. The most common TEAEs (≥ 3%) leading to dose modification were ALT increased (5%), AST increased (5%), and neutrophil count decreased (4%). The majority of adverse events leading to dose modification occurred in the first three months of treatment.

Permanent discontinuation of VITRAKVI for treatment emergent adverse events occurred in 9% of patients. The TEAEs that led to discontinuation of VITRAKVI and occurred in more than one patient were dehydration, malignant neoplasm progression, increased ALT, and increased AST.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of VITRAKVI was evaluated in 279 patients (overall safety population) who received at least one dose of VITRAKVI in one adult dose-finding trial [Study 1 (LOXO-TRK-14001) (n= 75)], one single arm trial [Study 2 (NAVIGATE) (n=116)], and one pediatric trial [Study 3 (SCOUT) (n=88)]. The median time on treatment was 6.8 months (range: 0.03 month to 51.6 months). One-hundred fifty (54%) patients were exposed to VITRAKVI for ≥ 6 months and 83 (30%) patients were exposed for ≥ 1 year. The majority of patients had an unresectable or metastatic solid tumour, including metastatic (72%) and locally advanced (18%) disease extent at enrollment.

Overall, patients had a median age of 46 years (range: 0.1 year to 84 years) with 33% of patients being pediatric patients. Forty-eight of patients were males and 74% were white.

The majority (86%) of adult patients (18 years and older) received 100 mg VITRAKVI taken twice daily as their starting dose. Three pediatric dose levels were evaluated with 85% of pediatric patients having received a starting dose of 100 mg/m^2 (with a maximum of 100 mg) taken twice daily. The dose ranged from 50 mg daily to 200 mg twice daily in adults and 9.6 mg/m^2 twice daily to 120 mg/m^2 twice daily in pediatric patients.

Table 3: Treatment-Emergent Adverse Events Occurring in ≥10% of Patients Treated with VITRAKVI (Pooled Analysis)

System Organ Class[a]	VITRAKVI n=279	
	All Grades n (%)	Grade 3-4 n (%)
General Disorders and Administrative Site Conditions		
Fatigue	92 (33)	7 (3)
Pyrexia	65 (23)	5 (2)
Edema peripheral	44 (16)	0 (0)
Nervous System Disorders		
Dizziness	73 (26)	3 (1)
Headache	42 (15)	1 (<1)
Gastrointestinal Disorders		
Nausea	69 (25)	2 (1)
Vomiting	71 (25)	2 (1)
Constipation	76 (27)	1 (<1)
Diarrhea	73 (26)	4 (1)
Abdominal pain	38 (14)	5 (2)

Table 3: Treatment-Emergent Adverse Events Occurring in ≥10% of Patients Treated with VITRAKVI (Pooled Analysis)

System Organ Class[a]	VITRAKVI n=279	
	All Grades n (%)	Grade 3-4 n (%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	45 (16)	2 (1)
Myalgia	48 (17)	3 (1)
Muscular weakness	28 (10)	2 (1)
Back pain	35 (13)	2 (1)
Pain in extremity	38 (14)	2 (1)
Blood and Lymphatic Disorders		
Anemia	71 (25)	26 (9)
Neutrophil count decreased	37 (13)	19 (7)
Lymphocyte count decreased	36 (13)	12 (4)
Leukocyte count decreased	31 (11)	1 (<1)
Investigations		
Alanine aminotransferase increased	79 (28)	9 (3)
Aspartate aminotransferase increased	71 (25)	7 (3)
Weight increased	40 (14)	10 (4)
Blood creatinine increased	28 (10)	2 (1)
Metabolism and nutrition disorders		
Decreased appetite	34 (12)	4 (1)
Hypoalbuminemia	28 (10)	2 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	83 (30)	1 (<1)
Dyspnea	47 (17)	7 (3)
Nasal congestion	32 (11)	0 (0)
Infections and infestations		
Upper respiratory tract infection	36 (13)	0 (0)
Urinary tract infection	32 (11)	4 (1)

[a] Adverse events are identified using MedDRA version 22.0 and graded according to CTCAE version 4.03.

Additional Information in Selected Adverse Reactions

Neurologic/Psychiatric events

In the overall safety database (n=279), neurologic/psychiatric TEAEs of any grade were reported in 63% of patients. Neurologic/psychiatric adverse events occurring in > 5% of patients included dizziness (26%), headache (15%), mood disorders (14%), cognitive impairment (11%), sleep disorders (10%), gait disturbance (6%), paresthesia (6%), dysgeusia (6%), and peripheral sensory neuropathy (5%). Mood disorders is collectively made up of the adverse events anxiety (5%), depression (4%), agitation (3%), irritability (3%), depressed mood (<1%), and euphoric

mood (<1%). Cognitive impairment is collectively made up of the adverse events memory impairment (4%), confusional state (3%), disturbance in attention (3%), delirium (2%), cognitive disorder (1%), aphasia (1%), hallucination (2%), mental status change (1%), amnesia (<1%), and mental impairment (<1%). Sleep disorders is collectively made up of the adverse events insomnia (7%), somnolence (3%), and sleep disorder (<1%). Grade 3 and Grade 4 neurologic/psychiatric events were reported in 11% and < 2% of patients, respectively. Events led to dose modification (interruption or reduction) in 30 (11%) patients.

Transaminase Elevations

In the overall safety database (n=279), TEAEs of ALT increased occurred in 28% of patients, and AST increased occurred in 25% of patients. The maximum grade transaminase elevations observed were Grade 4 ALT increased in 2 patients (1%), Grade 4 AST increased in 1 patient (<1%), Grade 3 ALT increased in 7 (3%) patients and Grade 3 AST increased in 6 (2%) patients. The incidence of transaminase elevations was higher in pediatric compared with adult patients (see Clinical Trial Adverse Reactions (Pediatrics)).

ALT and AST increases leading to study drug interruption or dose modifications occurred in 14 (5%) patients and 13 (5%) patients, respectively. Increased transaminases led to permanent discontinuation of VITRAKVI in 2% of patients.

7.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and other Quantitative Data

Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Clinically Relevant Laboratory Abnormalities based on Laboratory Reports

Laboratory Parameter* (SOC/PT)	Overall Safety Analysis Set n=279, n (%)		
	Grade 3	Grade 4	All Grades**
Investigations			
Aspartate aminotransferase (AST) increased	10 (4)	2 (1)	178 (64)
Alanine aminotransferase (ALT) increased	9 (3)	3 (1)	176 (63)
Hypoalbuminemia	7 (3)	0	154 (55)
Blood alkaline phosphatase increased	7 (3)	0	142 (51)
Blood and lymphatic system disorders			
Hemoglobin decreased	28 (10)	0	216 (77)
Neutrophil count decreased	21 (8)	6 (2)	93 (33)
Leukocyte count decreased	5 (2)	1 (<1)	109 (39)

* Includes laboratory abnormalities that were reported as treatment-related adverse events for at least 5% of patients. Data are based on the maximum toxicity grade reported during the study, including patients who had no change from baseline grade.
**NCI CTCAE version 4.03

7.4 Clinical Trial Adverse Reactions (Pediatrics)

Of 279 patients treated with VITRAKVI, 92 (33%) patients were pediatrics, including 33 infants and toddlers aged up to 23 months, 38 children aged 2 to 11 years, and 21 adolescents aged 12 to < 18 years. The safety profile in the pediatric population was generally consistent in the types of reported adverse events to those observed in the adult population. A majority of adverse events were Grade 1 or 2 in severity and were resolved without VITRAKVI dose modification or discontinuation. The TEAEs that were more frequent in pediatric patients compared with adult patients regardless of attribution (≥ 10% difference) included vomiting (42% versus 17% in adults); transaminase elevations (ALT 37% versus 24% and AST 32% versus 22%); neutrophil count decreased (29% versus 5%); diarrhea (34% versus 22%); pyrexia (43% versus 13%); platelet count decreased (13% versus 3%); upper respiratory tract infection (23% versus 8%); leukocyte count decreased (20% versus 7%); nasopharyngitis (16% versus 6%); otitis media (13% versus 1%) and rhinitis (14% versus 1%). Treatment-emergent adverse events reported in the infant and toddler subgroup (n=33) at a higher incidence than in the other pediatric subgroups included vomiting (n=19); cough (n=15); diarrhea (n=19); pyrexia (n=26); ALT increased (n=15); neutrophil count decreased (n=15); and anemia (n=10).

Clinical Trial Adverse Reactions (Geriatrics)

Of 279 patients in the overall safety population who received VITRAKVI, 54 (19%) patients were ≥ 65 years of age and 13 (5%) patients were ≥ 75 years of age. The safety profile in elderly patients (≥ 65 years) was generally consistent with that seen in adult patients < 65 years of age. The TEAEs that were more frequent in patients ≥ 65 years of age included fatigue, anemia, dizziness, fall, gait disturbance, and hyponatremia.

8. DRUG INTERACTIONS

8.1 Overview

Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Coadministration of VITRAKVI with strong CYP3A inhibitors, P-gp and BCRP inhibitors may increase larotrectinib plasma concentrations.

Coadministration of VITRAKVI with strong CYP3A and P-gp inducers may decrease larotrectinib plasma concentrations.

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

In vitro studies indicate that larotrectinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. *In vitro*, larotrectinib is a metabolism-dependent irreversible inhibitor of CYP3A4/5 (contributing to weak inhibition clinically [see DRUG INTERACTIONS: Drug-Drug Interactions - Effects of Larotrectinib on Other Agents - CYP3A Substrates]).

In vitro studies indicate that larotrectinib induces CYP2B6, but does not induce CYP1A2.

In vitro studies indicate that larotrectinib does not inhibit the transporters BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, MATE1 and MATE2-K at clinically relevant concentrations.

8.2 Drug-Drug Interactions

Effects of Other Agents on Larotrectinib

CYP3A, P-gp and BCRP Inhibitors

Clinical data in healthy adult subjects indicate that coadministration of a single 100 mg VITRAKVI dose with itraconazole (a strong CYP3A inhibitor and P-gp and BCRP inhibitor) increased larotrectinib C_{max} and AUC by 2.8-fold and 4.3-fold, respectively.

Avoid coadministration of strong CYP3A4 inhibitors with VITRAKVI (e.g. atazanavir, clarithromycin, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, voriconazole, grapefruit or grapefruit juice). If coadministration of a strong CYP3A4 inhibitor cannot be avoided, reduce the VITRAKVI dose by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the VITRAKVI dose taken prior to initiating the CYP3A4 inhibitor.

Clinical data in healthy adult subjects indicate that coadministration of a single 100 mg VITRAKVI dose with a single dose of rifampin (a P-gp and BCRP inhibitor) increased larotrectinib C_{max} and AUC by 1.8-fold and 1.7-fold, respectively.

CYP3A and P-gp Inducer

Clinical data in healthy adult subjects indicate that coadministration of a single 100 mg VITRAKVI dose with multiple doses of rifampin (a strong CYP3A and P-gp inducer) decreased larotrectinib C_{max} and AUC by 71% and 81%, respectively. Avoid coadministration of strong CYP3A4 inducers with VITRAKVI (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, or rifampin). If coadministration of a strong CYP3A4 inducer cannot be avoided, double the VITRAKVI dose. After the inducer has been discontinued for 3 to 5 elimination half-lives, resume the VITRAKVI dose taken prior to initiating the CYP3A4 inducer.

Gastric pH-elevating Agents

Larotrectinib has pH-dependent solubility. *In vitro* studies show that in liquid volumes relevant to the gastrointestinal tract (GI) larotrectinib at the recommended dose is fully soluble over entire pH range of the GI tract. Therefore, larotrectinib is unlikely to be affected by pH-modifying agents.

Effects of Larotrectinib on Other Agents

CYP3A Substrates

Larotrectinib is a weak CYP3A inhibitor. Clinical data in healthy adult subjects indicate that coadministration of VITRAKVI (100 mg twice daily for 10 days) increased the C_{max} and AUC of midazolam (a sensitive CYP3A substrate) 1.7-fold compared to midazolam alone.

Exercise caution with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. fentanyl, cyclosporine, dihydroergotamine, pimozide, quinidine, sirolimus, or tacrolimus) in patients taking VITRAKVI. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking VITRAKVI, monitor patients for increased adverse reactions; dose modification of the CYP3A substrates may be considered.

8.3 Drug-Food Interactions

Larotrectinib may be administered with or without food (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics - Absorption). Avoid grapefruit or grapefruit juice as these may also increase plasma concentrations of larotrectinib.

8.4 Drug-Herb Interactions

Avoid hypericum perforatum (a CYP3A4 inducer), also known as St. John's wort, as it may decrease plasma concentrations of larotrectinib.

NOC/c

9. ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Larotrectinib is an orally-bioavailable, adenosine triphosphate (ATP)-competitive, potent and highly selective Tropomyosin Receptor Kinase (TRK) kinase inhibitor. Larotrectinib targets the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively. Larotrectinib has minimal activity with off-target kinases tested.

In-frame gene fusion events resulting from chromosomal rearrangements of the human genes *NTRK1*, *NTRK2*, and *NTRK3* lead to the formation of oncogenic TRK fusion proteins. These resultant novel chimeric oncogenic proteins are aberrantly expressed driving constitutive kinase activity subsequently activating downstream cell signalling pathways involved in cell proliferation and survival leading to TRK fusion cancer.

Larotrectinib demonstrated potent inhibition of TRK proteins and inhibition of proliferation of cell lines containing *NTRK* gene fusions in a concentration-dependent manner. In TRK fusion-driven mouse xenograft models larotrectinib treatment induced significant tumour growth inhibition.

Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to larotrectinib include G623R, G696A, and F617L.

9.2 Pharmacodynamics

Cardiac Electrophysiology

Potential effects of larotrectinib on the QT interval were examined with the use of concentration-response modeling of the QTc data. The model was built on a single data set containing 36 healthy adult subjects receiving single doses ranging from 100 mg to 900 mg (n=6 per treatment arm receiving larotrectinib). Based on the model, larotrectinib at C_{max} did not prolong the QT interval to any clinically relevant extent.

9.3 Pharmacokinetics

Table 5 - Summary of Larotrectinib Pharmacokinetic Parameters in Adult Cancer Patients at Steady State[a]

	C_{max}	T_{max} (h)	$T_{½}$ (h)	AUC_{0-24}	CL	Vd
100 mg BID Mean[b]	914 ± 445 ng/mL	1.14 ± 1.46	2.99 ± 1.52	5410 ± 3813 ng*h/mL	57.33 ± 39,87 L/h	241.7 ± 217.92 L

Abbreviations: AUC = area under the curve; C_{max} = maximum drug concentration in plasma after dose; CL = Clearance; $T_{½}$ = Terminal half life; T_{max} = Time to reach C_{max}; Vd = Volume distribution

[a] steady-state is reached within 8 days

[b] steady-state arithmetic mean

Absorption

VITRAKVI is available as a capsule and oral solution formulation. In healthy adult subjects, the AUC of larotrectinib in the oral solution formulation was similar to the capsule; C_{max} was 36% higher with the oral solution formulation.

The mean absolute bioavailability of larotrectinib was 34% (range: 32% to 37%) following a single 100 mg oral dose.

C_{max} and AUC in the capsule formulation were dose proportional in healthy adult subjects up to 400 mg and slightly greater than proportional at doses of 600 to 900 mg. Systemic accumulation is 1.6 fold at steady state.

Effect of Food

Larotrectinib C_{max} was reduced by approximately 35% and there was no effect on AUC in healthy subjects administered VITRAKVI after a high-fat and high-calorie meal compared to the C_{max} and AUC after overnight fasting.

Distribution

Binding of larotrectinib to human plasma proteins in vitro was approximately 70% and was independent of drug concentration. The blood-to-plasma concentration ratio was approximately 0.9.

Metabolism

Larotrectinib is metabolized predominantly by CYP3A4/5 (see DRUG INTERACTIONS). Following oral administration of a single 100 mg dose of radiolabeled larotrectinib to healthy adult subjects, unchanged larotrectinib (19%) and O-glucuronide larotrectinib that is formed following loss of the hydroxypyrrolidine-urea moiety (26%) were the major circulating radioactive drug components in plasma.

Elimination

Following oral administration of 100 mg radiolabeled larotrectinib as an oral solution to healthy adult subjects, 58% (5% unchanged) of the administered radioactivity was recovered in feces and 39% (20% unchanged) was recovered in urine.

Special Populations and Conditions

Pediatrics:

Based on population pharmacokinetic analyses exposure (C_{max} and AUC) in pediatric patients (1 month to <3 months of age) at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID was 3-fold higher than in adults (≥18 years of age) given the dose of 100 mg BID. At the recommended dose, the C_{max} in pediatric patients (≥3 months to <12 years of age) was higher than in adults, but the AUC was similar to that in adults. For pediatric patients older than 12 years of age, the recommended dose is likely to give similar C_{max} and AUC as observed in adults.

Geriatrics:

Based on population pharmacokinetic analyses, C_{max} and AUC in patients >65 years were similar to those in younger patients (<65 years).

Sex:

Gender had no significant effect on the systemic exposure of larotrectinib based on population pharmacokinetic analyses.

Ethnic Origin:

Race had no significant effect on the systemic exposure of larotrectinib based on population pharmacokinetic analyses. Caucasians accounted for 72% of the analysis population.

Hepatic Insufficiency:

A pharmacokinetic study was conducted in subjects with mild (Child Pugh A), moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment, and in healthy adult control subjects with normal hepatic function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib $AUC_{0\text{-}inf}$ was observed in subjects with mild, moderate and severe hepatic impairment of 1.3, 2 and 3.2-fold respectively versus those with normal hepatic function. C_{max} was observed to increase slightly by 1.1, 1.1 and 1.5-fold respectively. Reduce the starting dose of VITRAKVI by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild (Child-Pugh A) hepatic impairment.

Renal Insufficiency:

A pharmacokinetic study was conducted in subjects with end stage renal disease requiring dialysis, and in healthy adult control subjects with normal renal function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib Cmax and $AUC_{0\text{-}inf}$, of 1.25 and 1.46-fold respectively was observed in renally impaired subjects versus those with normal renal function. No dose adjustment is recommended for patients with renal impairment of any severity.

Body Weight:

Body weight from 5.0 kg to 179.4 kg had no significant effect on the AUC of larotrectinib based on population pharmacokinetic analyses. The mean AUC of larotrectinib may be increased in children weighing <5.0 kg (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics – Special Populations and Conditions - Pediatrics:).

10. STORAGE, STABILITY AND DISPOSAL

Capsules

Store capsules at room temperature 15°C to 30°C.

Oral solution

Store solution refrigerated at 2°C to 8°C. Do not freeze.
Discard 30 days after first opening.

PART II: SCIENTIFIC INFORMATION

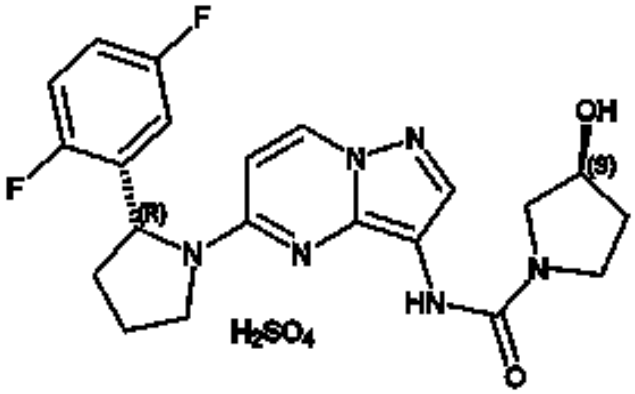
VITRAKVI, indicated for:
- the treatment of adult and pediatric patients with solid tumours:

- *have a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion without a known acquired resistance mutation,*
- *are metastatic or where surgical resection is likely to result in severe morbidity, and*
- *have no satisfactory treatment options*

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VITRAKVI please refer to Health Canada's Notice of Compliance with conditions - drug products web site (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php).

11. PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	larotrectinib sulfate
Chemical name:	(3S)-N-{5-[(2R)-2-(2,5-Difluorophenyl)-1-pyrrolidinyl]pyrazolo[1,5-a]pyrimidin-3-yl}-3-hydroxy-1-pyrrolidinecarboxamide sulfate
Molecular formula and molecular mass:	$C_{21}H_{24}F_2N_6O_6S$ 526.51 g/mol
Structural formula:	
Physicochemical properties:	Larotrectinib is a crystalline sulfate salt, appearing as an off-white to yellow to pinkish yellow solid. The solubility of larotrectinib sulfate is pH dependent, having > 10 mg/mL solubility below pH 1.5, ~ 2 – 3 mg/mL solubility at pH 2.5, and dropping to ~1 mg/mL above pH 3.5. Larotrectinib sulfate has only been observed as a single polymorph.

NOC/c

12. CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Three ongoing multicenter, open-label, single-arm clinical studies in patients with advanced cancer contributed patients to a pooled efficacy analysis evaluating VITRAKVI for the treatment of adult and pediatric patients with unresectable or metastatic solid tumours with a Neurotrophic Tyrosine Receptor Kinase *(NTRK)* gene fusion, as follows (see Table 6):

1) Phase 1 adult dose-finding study (Study 1 [LOXO-TRK-14001] [n=13);
2) Phase 2 adult and pediatric "basket" study (Study 2 [NAVIGATE] [n=98]); and
3) Phase 1/2 pediatric dose-finding/efficacy and safety study (Study 3 [SCOUT] [n=53]).

Enrollment to Study 1 and the Phase 1 portion of Study 3 was not restricted to patients with a documented *NTRK* gene fusion but patients with prospectively identified *NTRK* gene fusions were included in the pooled efficacy analysis. Patients enrolled to Study 2 were required to have tropomyosin receptor kinase (TRK) fusion cancer. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity. Protocol amendments excluded patients with prior progression on approved or investigational kinase inhibitors with anti-TRK activity from Studies 2 and 3.

The assessment of efficacy is based on an analysis of 164 patients comprising an extended primary analysis set (ePAS). The ePAS includes the first 55 patients with solid tumours with an *NTRK* gene fusion who were enrolled across the three clinical studies (the primary analysis set [PAS]) plus additional patients who subsequently started treatment and with ≥ 6 months follow up at the July 15, 2019 cutoff date. Patients in the ePAS were required to have a documented *NTRK* gene fusion as determined by local testing; a non-Central Nervous System (non-CNS) primary tumour with ≥ 1 measurable lesion at baseline, per investigator assessment based on Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 (v1.1); and to have received ≥ 1 dose of VITRAKVI.

Identification of *NTRK* gene fusions was prospectively determined in local certified laboratories primarily using next generation sequencing (NGS), in some cases, by fluorescence in situ hybridization (FISH) and by reverse transcription-polymerase chain reaction (RT-PCR) in one case.

The majority of adult patients received a starting dose of VITRAKVI of 100 mg orally twice daily and the majority of pediatric patients received VITRAKVI 100 mg/m^2 up to a maximum dose of 100 mg orally twice daily until unacceptable toxicity or disease progression.

Table 6: Summary of Clinical Studies Contributing Patients to the Pooled Efficacy Analysis Set (ePAS)

Study	Study Design and Patient Population	Dosing regimen	No. of Patients in the ePAS n=164 (n)	Median Age of Patients in the ePAS, year (range)	Sex of Patients in the ePAS (female / male)	Tumour Types of Patients in the ePAS
Study 1 (LOXO-TRK-14001)	• Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours harbouring an *NTRK* gene fusion • Adult patients (≥ 18 years) with advanced solid tumours	Doses up to 200 mg once or twice daily	13	55.0 (28.0 – 80.0)	6/7	Salivary gland (n=3) GIST[a] (n=2) Lung (n=1) Soft tissue sarcoma (n=2) Thyroid (n=4) Unknown primary cancer (n=1)
Study 2 (NAVIGATE)	• Phase 2 multinational, open label, tumour "basket" study • Adult and pediatric patients ≥ 12 years with advanced solid tumours harbouring an *NTRK* gene fusion	100 mg twice daily	98	55.5 (6.0-84.0)	52/46	Salivary gland (n=18) Soft tissue sarcoma (n=16) Colorectal (n=8) Thyroid (n=23)[c] Melanoma (n=6)[c] Lung (n=12) GIST[a] (n=2) Cholangiocarcinoma (n=2) Pancreas (n=2) Breast, non-secretory (n=3)[c] Breast, secretory (n=2) Other (n=4)[d]
Study 3 (SCOUT)	• Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours harbouring an *NTRK* gene fusion • Pediatric patients ≥ 1 month to 21 years	Dosing based on adult equivalent of 100 or 150 mg BID, then 100 mg/m^2 twice daily (with a maximum of 100 mg twice daily)	53	1.25 (0.05-19.92)	26/27	Infantile fibrosarcoma (n=32) Soft tissue sarcoma (n=18) Bone sarcoma (n=1) Congenital mesoblastic nephroma (n=1) Melanoma (n=1)

[a] GIST= gastrointestinal stromal tumour
[b] Brain metasteses observed in 1 Lung NSCLC patient (Study 1)
[c] Brain metastases observed in 5 Lung NSCLC patients, 1 SCLC Lung patient, 4 Thyroid patients; 2 Melanoma patients and 1 Breast (non-secretory patient (Study 2 'NAVIGATE')
[d]Other tumour types included Appendix (n=1), Bone Sarcoma (n=1), Hepatic (Hepatocellular Carcinoma] (n=1) and Prostate (n=1)

For the pooled efficacy analysis, the primary endpoint was overall response rate (ORR), while the duration of response (DOR) was a secondary endpoint, both determined by a blinded Independent Review Committee (IRC) according to RECIST, v1.1. Additional secondary efficacy outcomes assessed included time to first response. A lower boundary of 30% for ORR, considered to be clinically meaningful, was predefined as statistically significant for response. The ORR was defined as the proportion of patients with the best overall response of confirmed complete response (CR) or confirmed partial response (PR).

Baseline characteristics for the pooled 164 patients with solid tumours harbouring an *NTRK* gene fusion were as follows: median age 42 years (range 0.1-84 years); 34% < 18 years of age, 66% ≥ 18 years, and 21% > 65 years; 77% white and 49% male; and Eastern Cooperative Oncology Group (ECOG) Performance Status (ECOG PS) 0 - 1 (86%), 2 (12%) or 3 (2%). Seventy-four percent of patients had metastatic disease and 26% of patients had locally advanced, unresectable disease. Median time from diagnosis was 1.7 years (range: 0.02-31.5 years). Ninety-four percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. Of these, 77% had received prior systemic therapy with a median of 1 prior regimens received (range: 0-10). Twenty-seven percent of all patients had received 3 or more prior systemic therapies and 51% of all patients had received 1-2 prior systemic therapies. Twenty-two percent of all patients had received no prior systemic therapy.

The most common tumour types represented were soft tissue sarcoma (22%), infantile fibrosarcoma (20%), thyroid cancer (16%), salivary gland tumor (13%) and lung (8%). *NTRK* gene fusions were identified by NGS, FISH, and RT-PCR in 92.3%, 6.4%, and 1.3% of patients, respectively. The TRK fusions involved *NTRK1* (in 41% of patients), *NTRK2* (in 2%), or *NTRK3* (in 56%) and 31 unique upstream fusion partners. In nine patients (5%) with infantile fibrosarcoma who had a documented *ETV6* translocation identified by FISH, *NTRK3* gene fusions were inferred.

12.2 Study Results

In the ePAS, the overall response rate was 73% (95% confidence interval [CI]: 65, 79]. The ORR included a CR in 31 patients (19%), a surgical CR (sCR) in 8 (5%), and a PR in 80 (49%). With a median duration of follow-up of 15.7 months, the median DOR was not yet estimable. Seventy-six percent of responders (90 of 164 patients) were still in response, and the duration of response exceeded 6 months in 89%. The pooled efficacy results for overall response rate, best overall response, and duration of response are presented in Table 7.

Table 7: Efficacy Results for Pooled Efficacy Analysis Set (ePAS) (Best Overall Response and Duration of Response, IRC Assessment)

Efficacy Parameter	Pooled Analysis Set n=164
Overall Response Rate (ORR)[a] % (n) [95% CI]	73% (119) [65, 79]
Complete Response (CR)	19% (31)
Pathological Complete Response[b]	5% (8)
Partial Response (PR)	49% (80)
Duration of Response[c], Median, months [range]	NE [0+ to 50.6+]

IRC: Independent Review Committee; NE: not estimable; + denotes ongoing

[a] ORR according to RECIST 1.1

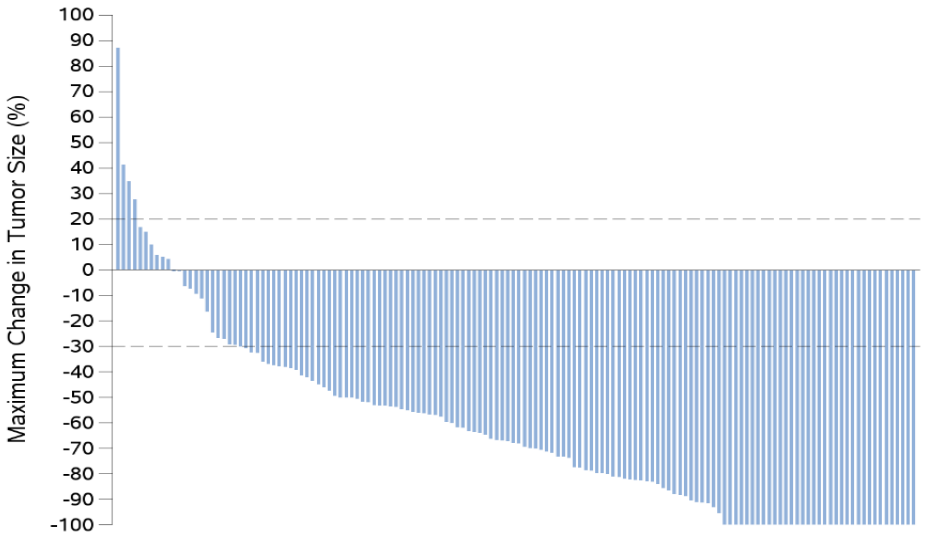
[b] A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation. The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1.

[c] Estimated using Kaplan-Meier method

The median time to first response was 1.8 months (range: 0.9 to 14.6 months) and 81% of responses occurred within the first 2 months of treatment which coincides with the timing of the first assessment protocol. ORR in the adult sub-population (n=109) was 63% and 91% in the pediatric sub-population (n=55).

Changes in target lesion size for individual patients are illustrated in the Waterfall plot in Figure 1.

Figure 1: Maximal Percent Change in Tumour Size within Target Lesions per RECIST v1.1 by Patient[a] (IRC Assessment)



IRC: Independent Review Committee
[a] Patients of the pooled analysis set with measurable disease in IRC and at least 1 post-baseline assessment (n = 106)

Additional efficacy results by tumour type and by *NTRK* gene fusion partner are presented in Table 8 and Table 9, respectively.

Table 8: Efficacy Results by Tumour Type (IRC Assessment) for Pooled Analysis Set (ePAS 4)

Tumour Type	n	ORR[a] % (95% CI)	DOR Range (months)	Rate (%) DOR at 12, 24 months[b]
Overall	164	73 (65, 79)	0.03+ to 50.6+	76, 67
Soft tissue sarcoma	36	81 (64, 92)	0.03+ to 50.6+	69, 69
Infantile fibrosarcoma	32	97 (84, 100)	1.58+ to 28.55+	72, 63
Thyroid	27	56 (35, 75)	3.65+ to 32.89+	93, 58
Salivary gland	21	86 (64, 97)	1.94+ to 44.68+	94, 87
Lung	13	77 (46, 95)	3.65 to 36.83+	62, 62
Colon	8	38 (9, 76)	5.42+ to 20.67+	50%, NR
Melanoma	7	43 (10, 82)	1.87+ to 23.20+	50, NR
Breast	5	60 (15, 95)	5.59+ to 9.23+	NR, NR
GIST	4	100 (40, 100)	9.46 to 31.05+	75, 38
Bone sarcoma	2	50 (1, 99)	9.49, 9.49[c]	0, 0
Cholangiocarcinoma	2	0 (NC)	NA	NA
Pancreas	2	0 (NC)	NA	NA
Appendix	1	0 (NC)	NA	NA
Cancer of unknown primary	1	100 (3, 100)	7.39, 7.39[c]	0, 0
Congenital mesoblastic nephroma	1	100 (3, 100)	20.83+ to 20.83+[c]	100%, NR
Hepatic	1	0 (NC)	NA	NA
Prostate	1	0 (NC)	NA	NA

CI: confidence interval; GIST: gastrointestinal stromal tumour; IRC: Independent Review Committee; NA: not available; NC: not calculated; NR: not reached; ORR: overall response rate; + denotes ongoing

[a] ORR according to RECIST 1.1

[b] Estimated using Kaplan-Meier method

[c] Based on a single subject

Table 9: Efficacy Results by *NTRK* Gene Fusion Partner for Pooled Efficacy Analysis Set (ePAS 4)

***NTRK* Gene Fusion Partner**	**n**	**ORR[a] % (95% CI)**	**DOR Range (months)**
Overall	164	73 (65, 79)	0.03+ to 50.6+
ETV6-NTRK3	80	85 (75, 92)	0.03+ to 44.7+
Inferred ETV6-NTRK3	10	90 (55, 100)	1.6+ to 28.6+
TPM3-NTRK1	30	73 (54, 88)	1.05 to 27.5+
LMNA-NTRK1	13	62 (32, 86)	2.8+ to 50.6+
TPR-NTRK1	5	20 (1, 72)	8.2[b]
EML4-NTRK3	4	25 (1, 81)	7.9[b]
IRF2BP2-NTRK1	4	100 (40, 100)	3.7 to 36.8+
EPS15-NTRK1	2	100 [16,100]	9.3+ to 9.5
SQSTM1-NTRK1	2	100 (16, 100)	9.9 to 12.9+
SQSTM1-NTRK3	2	50 [1, 99]	17.4+
ARNT2-NTRK3	1	0 [NC]	NA
ATP1A4-NTRK1	1	0 [NC]	NA
CD74-NTRK1	1	100 (3,100)	3.65[b]
CLIP1-NTRK1	1	0 [NC]	NA
CTRC-NTRK1	1	0 (NC)	NA
DDR2-NTRK1	1	0 [NC]	NA
DIAPH1-NTRK1	1	0 [NC]	NA
GNAQ-NTRK2	1	0 (NC)	NA
GON4L-NTRK1	1	0 (NC)	NA
IQGAP1-NTRK1	1	0 [NC]	NA
MYO5A-NTRK3	1	100 (3, 100)	3.7[b]
NFASC-NTRK1	1	0 [NC]	NA
PDE4DIP-NTRK1	1	100 (3, 100)	3.6+[b]
PLEKHA6-NTRK1	1	0 (NC)	NA
PPL-NTRK1	1	100 (3, 100)	28.2+[b]
RBPMS-NTRK2	1	100 (3, 100)	9.3+[b]
SPECC1L-NTRK3	1	100 (3, 100)	19.1+[b]
STRN-NTRK2	1	100 (3, 100)	5.6[b]
TFG-NTRK3	1	100 (3, 100)	3.9+[b]
TPM4-NTRK3	1	100 (3, 100)	25.6[b]
TRAF2-NTRK2	1	0 [NC]	NA
TRIM63-NTRK1	1	100 (3, 100)	1.9+[b]

NA: not available; NC: not calculated; + denotes ongoing
[a] ORR according to RECIST 1.1
[b] Based on a single subject

Patients with CNS Tumors

Twenty-four patients with primary CNS tumors and measurable disease at baseline were enrolled in study 2 ("NAVIGATE") and in study 3 ("SCOUT"). Baseline characteristics for the 24 patients with primary CNS tumors with an NTRK gene fusion assessed by investigator were as follows: median age 8 years (range 1.3-79 years); 20 patients < 18 years of age and 4 patients ≥ 18 years, and 19 patients white and 11 patients male; and ECOG PS 0-1 (22 patients), or 2 (1 patient). All CNS tumor patients had received prior cancer treatment (surgery, radiotherapy and/or previous systemic therapy). There was a median of 1 prior systemic treatment regimen received. Tumor responses for primary CNS tumors were assessed by the investigator using Response Assessment in Neuro Oncology (RANO) Criteria or Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

Of the 24 patients with primary CNS tumors, confirmed response was observed in 5 patients (21%) with 2 of the 24 patients (8%) being complete responders and 3 (12.5%) being partial responders. At a median follow-up time of 10.1 months, the median duration of response was 4.9 months (1.7+ months, 10.1+ months). Further, 17 patients (71%) had stable disease. Two patients (8%) had a progressive disease.

13. NONCLINICAL TOXICOLOGY

General Toxicity

Repeated-dose toxicity was assessed in studies with daily oral administration up to 13-weeks in rats and monkey. Dose limiting skin lesions were only seen in rats and were primarily responsible for mortality and morbidity. In rats, severe toxicity was observed at doses corresponding to human AUC at the recommended clinical dose. Clinical signs of gastrointestinal toxicity including emesis, were dose limiting in monkeys. No relevant systemic toxicity were observed in monkeys at exposures which correspond to >10-times the human AUC at the recommended clinical dose.

Increased body weight, increased food consumption, and elevated serum liver enzymes (ALT and/or AST) are additional relevant findings that were observed in both species.

Genotoxicity and Carcinogenicity

Larotrectinib was not mutagenic in bacterial reverse mutation (Ames) assays and in in vitro mammalian mutagenesis assays. Larotrectinib was negative in the *in vivo* mouse micronucleus test.

Carcinogenicity studies have not been performed with larotrectinib.

Reproductive and Developmental Toxicology

Reproduction Toxicity

Fertility studies with larotrectinib have not been conducted. In 13-week repeated-dose studies, larotrectinib had no effects on spermatogenesis in rats and on the histopathology of male reproductive organs in rats and monkeys at doses corresponding to approximately 7-times (rats) and 10-times (monkeys) the human AUC at the recommended clinical dose.

In a 1-month study in female rats, fewer corpora lutea, increased incidence of anestrus and decreased uterine weight with uterine atrophy were observed at doses corresponding to approximately 8-times the human AUC at the recommended clinical dose; these effects were

reversible. No effects on reproductive organs were seen in the 13-week study in rats and monkeys at doses corresponding to approximately 3 times (rats) and approximately 17-times (monkeys) the human AUC at the recommended clinical dose.

Development

In embryo-fetal development studies where pregnant rats and rabbits were dosed with larotrectinib during the period of organogenesis, malformations were observed at maternal exposures that were approximately 9- and 0.6- times, respectively, those observed at the clinical dose of 100 mg twice daily. Larotrectinib was not embroytoxic up to maternally toxic doses. Larotrectinib crosses the placenta in both species and can be detected in blood samples obtained from fetuses at termination.

Juvenile Toxicity

Larotrectinib was administered in a juvenile toxicity study in rats at twice daily doses of 0.2, 2 and 7.5 mg/kg from postnatal day (PND) 7 to 27 and at twice daily doses of 0.6, 6 and 22.5 mg/kg between PND 28 and 70. The dosing period was equivalent to human pediatric populations from newborn to adulthood. The lowest dose (0.2/0.6 mg/kg BID), equivalent to 0.02-fold the recommended clinical exposure, was considered the NOAEL. At doses ≥2/6 mg/kg BID (0.5-fold the recommended clinical exposure), increased mortality, neuronal effects (increased incidence of partially closed eyelids, lower hindlimb grip strength and foot splay), decreased growth (shorter tibial length and lower body weight gain with lower food intake) and delay in sexual development were noted. At doses 7.5/22.5 mg/kg BID (3-fold the recommended clinical exposure), central nervous system-related signs including head flick and circling, increased escape time and number of errors in a maze swim test when the original path is reversed, skin lesions, and swollen abdomen (females) were noted. Lower fertility was noted in animals at 3-times the recommended clinical exposure.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

VITRAKVI®

Larotrectinib capsules

Larotrectinib oral solution

Read this carefully before you start taking VITRAKVI and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about VITRAKVI.

"For the following indication VITRAKVI has been approved *with conditions* (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional."

WHAT IS VITRAKVI USED FOR?

VITRAKVI is indicated for children and adults. It can treat solid tumours that have a Neurotropic Tyrosine Receptor Kinase (*NTRK*) gene fusion. The *NTRK* gene fusion should not have a known resistance mutation. It can treat cancers that have spread to different parts of the body. Or, it can treat cancers where removal is likely to cause serious problems. VITRAKVI is for patients without other treatment choices.

To benefit from VITRAKVI, the patient must have a tumour that has an *NTRK* gene fusion. This can be checked by a test that is done before you start VITRAKVI.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does VITRAKVI work?

TRK fusion cancer always has a change in a gene called “Neurotrophic Tyrosine Receptor Kinase” (NTRK). The alteration in this gene causes the body to make a protein called “TRK fusion”. TRK fusion proteins can lead to uncontrolled cell growth and cancer.

VITRAKVI stops the TRK fusion proteins from working and may slow or stop the cancer from growing. It may also help to shrink the cancer.

What are the ingredients in VITRAKVI?

Medicinal ingredient: larotrectinib (as larotrectinib sulfate)

Capsules

Non-medicinal ingredients: ammonia solution, dimethicone, FD&C Blue #2 aluminum lake, gelatin, propylene glycol, shellac, titanium dioxide.

Oral Solution

Non-medicinal ingredients: citric acid, hydroxypropyl betadex, glycerol, methylparahydroxybenzoate, natural flavour, potassium sorbate, propylene glycol, purified water, sodium citrate, sodium dihydrogen phosphate, sorbitol, sucrose.

VITRAKVI comes in the following dosage forms:

Capsules: 25 mg and 100 mg
Oral solution: 20 mg/mL

Do not use VITRAKVI if:

- you are allergic to larotrectinib or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VITRAKVI. Talk about any health conditions or problems you may have including if you:

- Have liver disease

Other warnings you should know about:

Take VITRAKVI only under the care of a doctor who knows how to use anti-cancer drugs.

Female Patients: Pregnancy and Breast-feeding Information

Talk to your healthcare provider before taking VITRAKVI if you are pregnant, may become pregnant or are breast-feeding.

- Avoid getting pregnant when on VITRAKVI. There may be a risk of harm or birth defects to the baby.
- Before starting on VITRAKVI, your doctor should make sure that you are not pregnant.

- Use effective birth control while taking VITRAKVI and for at least one month after the last dose. Ask your doctor about the best birth control method for you.

Tell your doctor right away if you become pregnant while taking VITRAKVI or in the first month after your last dose.

It is not known if VITRAKVI passes into breast milk. Do not breast-feed while taking VITRAKVI and for one week after the last dose.

Male Patients: Do not father a child while VITRAKVI is in your body

Avoid fathering a child by using effective birth control methods. Do this during treatment with VITRAKVI and for at least one month after the final dose.

Driving and Using Machines

VITRAKVI may cause **Neurologic/Psychiatric Reactions**. This may make you feel dizzy or tired. It may affect your ability to walk and think clearly. If this happens, do not drive, cycle, or operate machinery. Wait until you know how you react to VITRAKVI before you do tasks which require special attention.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Some medicines can affect the level of VITRAKVI in your body. Also, VITRAKVI can affect the way some other medicines work. The medicines listed here may not be the only ones that could interact with VITRAKVI.

The following may interact with VITRAKVI:

- itraconazole, ketoconazole, posaconazole and voriconazole, clarithromycin – used to treat fungal and bacterial infections
- atazanavir, nelfinavir, rifabutin, ritonavir, saquinavir – used to treat HIV infection
- phenytoin, carbamazepine, phenobarbital – used to treat seizures
- St. John's wort – a herbal medicine, used to treat depression
- rifampin – used to treat bacterial infections
- cyclosporine, sirolimus, tacrolimus – used to prevent organ rejection in patients after transplantation
- quinidine – used to treat abnormal heart rhythms
- dihydroergotamine – used to treat migraine or cluster headache attack
- fentanyl – used for the treatment of chronic pain
- pimozide – an antipsychotic drug used to control motor or verbal tics

Avoid having grapefruit or its juice while on VITRAKVI. They may increase larotrectinib levels in your blood.

How to take VITRAKVI

- Take exactly as prescribed for you by your healthcare provider. Continue to take VITRAKVI unless your healthcare provider tells you to stop. Treatment may continue as long as it is helpful to you.
- If you can't take it as prescribed, or you feel you do not need it anymore, contact your healthcare provider right away.
- The total daily dose is **usually** divided in two and given twice a day. Some **adults** may get a reduced dose prescribed once a day.
- Take with or without food.

VITRAKVI is available as a capsule or oral solution. The capsules and oral solution are interchangeable. Your doctor will prescribe the correct dose.

- To take a VITRAKVI dose by:
    - Capsule: swallow whole with plenty of water. Do NOT open, chew, or crush.
    - Oral solution: swallow it by mouth or take it through a feeding tube. Always use a dosing syringe to measure the dose. Ask your pharmacist where to get a suitable dosing syringe.

Usual dose:

Depends on if you are a child or an adult. Your healthcare professional will monitor your condition. Your doctor may interrupt, reduce, increase, or stop your dose. This may occur based on your current health, if you have liver disease, take other medications, if your disease gets worse, or if you have too many side effects.

Pediatric (Children from one month up to 18 years old) Usual Daily Dose:

Your child's healthcare provider will work out the right daily dose in milligrams for your child. It is based on the child's height and weight. The daily prescribed amount is then divided in two and given twice a day. They can take:

- Capsule(s): by mouth.

  or

- Oral Solution: by mouth or through a feeding tube.

Adult (from 18 years old) Usual Daily Dose 200 mg:

- Capsule(s) 100 mg by mouth twice a day.

  or

- Oral Solution: 5 mL (100 mg) twice a day by mouth or through a feeding tube.

Pediatric and Adult **Maximum Daily Dose 200 mg:** 100 mg twice a day from capsules or the oral solution.

Overdose:

If you think you have taken too much VITRAKVI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take your next dose at the usual time. Do not take a double dose to make up for a missed dose.

If you or your child vomits (are sick) after taking VITRAKVI, just take the next dose at the usual time.

What are possible side effects from using VITRAKVI?

These are not all the possible side effects you may feel when taking VITRAKVI. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- feeling tired or weak
- dizziness, headache
- fever
- nausea, vomiting, constipation, diarrhea
- cough, shortness of breath, stuffy nose
- swelling or pain of arms, legs, hands, or feet
- muscle weakness
- muscle, joints, abdominal, or back pain
- decreased appetite
- weight gain

VITRAKVI can cause abnormal physical exam and blood test results. Your doctor will do some tests before, during and after your treatment. These tests include checking for **Neurologic/Psychiatric Reactions** and any **Liver Problems**. The doctor will interpret the results. They will tell you if there are any abnormalities in your tests that might need treatment.

Serious side effects and what to do about them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Anaemia (reduction in the number of red blood cells): Feel tired, looking pale and you may feel your heart pumping		✓	
Decreased Neutrophils and Leukocytes (white blood cells): Fever, fatigue, mouth ulcer, sore throat, or infections.		✓	
Liver Problems and increased liver enzymes: Loss of appetite, feeling sick or being sick, yellow skin, itching or pain in your liver area		✓	
Neurologic/Psychiatric Reactions including: Encephalopathy: Changes to the brain that cause problems with brain functioning. Delirium and memory impairment. Gait disturbance: Difficulty walking normally, balance disorder. Loss of consciousness, mental status change, tremor. Anxiety Paraesthesia: Abnormal sense of touch or tingling, burning feeling in your hands and feet.		✓	
COMMON			
Sepsis (serious infection due to bacteria in your blood): High fever, shaking, chills, weakness Fast heart rate. Rapid breathing.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- For capsules:
    - Store at room temperature 15 to 30°C.
- For oral solution
    - Store at 2°C to 8°C. Keep refrigerated. Do not freeze.
    - Discard 30 days after first opening.
- Keep out of reach and sight of children.
- Do not use this medicine after the expiry date which is stated on the carton and the bottle label after "EXP". The expiry date refers to the last day of that month.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

If you want more information about VITRAKVI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.bayer.ca or by calling Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This leaflet was prepared by

Bayer Inc.
2920 Matheson Blvd East
Mississauga, Ontario
L4W 5R6
Canada

Last Revised: May 11, 2021