PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **ROZLYTREK®**

entrectinib capsules

Capsules, 100 mg and 200 mg, Oral

Antineoplastic agent

ROZLYTREK, indicated for:

- the treatment of adult patients with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, and with no satisfactory treatment options

has been issued marketing authorization with conditions, pending the results of new information to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ROZLYTREK please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

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Date of Initial Approval:
February 7, 2020

Submission Control No: 227517

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)?

A 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.

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PART I: HEALTH PROFESSIONAL INFORMATION

NOC/c

1 INDICATIONS

ROZLYTREK (entrectinib) is indicated for the treatment of adult patients with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation, and with no satisfactory treatment options.

Clinical effectiveness is based on tumour objective response rate (ORR) and duration of response (DOR) in an integrated analysis of efficacy data from three studies in adults (see Clinical Trials).

Prior to initiation of ROZLYTREK therapy, *NTRK* fusion-positive status should be established using a validated test.

ROZLYTREK 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): Based on the limited data submitted and reviewed by Health Canada, the safety of ROZLYTREK in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see Warnings and Precautions, Musculoskeletal, Skeletal Fractures).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

NOC/c

2 CONTRAINDICATIONS

ROZLYTREK 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• ROZLYTREK may cause fetal harm when administered to a pregnant woman (see Warnings and Precautions, Special Populations, Pregnant Women) • ROZLYTREK may cause congestive heart failure (see Warnings and Precautions, Cardiovascular, Congestive Heart Failure)

NOC/c

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- A validated assay is required for the selection of patients with *NTRK* fusion-positive unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases. *NTRK* fusion-positive status should be established prior to initiation of ROZLYTREK therapy.

4.2 Recommended Dose and Dosage Adjustment

Dosage
ROZLYTREK hard capsules can be taken with or without food, swallowed whole, and must not be opened or dissolved.

The recommended dose of ROZLYTREK is 600 mg given orally, once daily (see Pharmacokinetics).

Duration of Treatment
It is recommended that patients are treated with ROZLYTREK until disease progression or unacceptable toxicity.

Dose Modifications
Management of adverse events may require temporary interruption, dose reduction, or discontinuation of treatment with ROZLYTREK, based on the prescriber's assessment of the patient's safety or tolerability.

The dose of ROZLYTREK may be reduced up to 2 times, based on tolerability. Table 1 provides general dose reduction advice for adult patients. ROZLYTREK treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily.

Table 1: Dose Reduction Schedule

Dose Reduction Schedule	Dose Level
Starting Dose	600 mg once daily
First dose reduction	400 mg once daily
Second dose reduction	200 mg once daily

Dose Modifications for Specific Adverse Reactions

Recommendations for ROZLYTREK dose modifications for specific adverse reactions are provided in Table 2 (see Warnings and Precautions and Adverse Reactions).

Table 2: Recommended Dose Modifications for Specified Adverse Drug Reactions

Adverse Drug Reaction	Severity *	Dose Modification
Anemia or Neutropenia	Grade 3 or Grade 4	Withhold ROZLYTREK until recovery to ≤ Grade 2 or to baseline, then resume treatment at same dose level or reduced dose by 1 level, as clinically needed.
Central Nervous System Effects	Grade ≥ 2	Withhold ROZLYTREK until recovery to ≤ Grade 1 or to baseline, then resume treatment at reduced dose by 1 level. If event recurs, further reduce dose by 1 level. For prolonged, severe, or intolerable events, discontinue as clinically appropriate.
Hepatotoxicity	Grade 3	Withhold ROZLYTREK until recovery to less than or equal to Grade 1 or to baseline. Resume at same dose if resolution occurs within 4weeks. Permanently discontinue if adverse reaction does not resolve within 4 weeks. Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.
	Grade 4	Withhold ROZLYTREK until recovery to less than or equal to Grade 1 or to baseline. Resume at reduced dose if resolution occurs within 4 weeks. Permanently discontinue if adverse reaction does not resolve within 4 weeks. Permanently discontinue for recurrent Grade 4 events.
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue ROZLYTREK.
Hyperuricemia	Symptomatic or Grade 4	Initiate urate-lowering medication. Withhold ROZLYTREK until improvement of signs or symptoms. Resume ROZLYTREK at same or reduced dose.

Adverse Drug Reaction	Severity *	Dose Modification
Syncope	Any Grade	Withhold ROZLYTREK until recovered, then resume treatment at reduced dose by 1 level. If event recurs, further reduce dose by 1 level or consider discontinuation as clinically appropriate.
Congestive Heart Failure	Any Grade	Withhold ROZLYTREK until recovered to ≤ Grade 1 and then resume treatment at reduced dose by 1 level, or discontinue as clinically appropriate.
QT Interval Prolongation	Grade 2	Withhold ROZLYTREK until recovered to baseline and then resume treatment at the same dose level.
	Grade 3	Withhold ROZLYTREK until recovered to baseline, then resume treatment at reduced dose by 1 level.
	Grade 4	Withhold ROZLYTREK until recovered to baseline, then resume treatment at reduced dose by 1 level. Discontinue treatment for signs and symptoms of serious arrhythmia.
Vision Disorders	Grade 2 or above	Withhold ROZLYTREK until improvement or stabilization. Resume at same dose or reduced dose, as clinically appropriate.

*Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Dose Modifications for Concomitant strong or moderate CYP3A inhibitors

The concomitant use of strong or moderate CYP3A inhibitors and ROZLYTREK in adults should be avoided or limited to 14 days or less. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, ROZLYTREK dose should be reduced to 100 mg once daily for use with strong CYP3A inhibitors and to 200 mg once daily for use with moderate CYP3A inhibitors.

After discontinuation of the concomitant strong or moderate CYP3A inhibitors, ROZLYTREK dose that was taken prior to initiating the strong or moderate CYP3A inhibitor can be resumed. A wash out period may be required for CYP3A4 inhibitors with long half-life (see Drug Interactions).

Dose Modifications for Concomitant CYP3A inducers

Co-administration of ROZLYTREK with CYP3A inducers should be avoided (see Drug Interactions).

Dose Modifications for Special Populations

Pediatric use

Health Canada has not authorized an indication for ROZLYTREK for pediatric use.

Geriatric use

No dose adjustment of ROZLYTREK is required in patients ≥ 65 years of age (see Pharmacokinetics, Special Populations and Conditions).

Renal Impairment
No dose adjustment is required in patients with mild or moderate renal impairment CrCl ≥30 mL/min calculated by the Cockroft-Gault equation). ROZLYTREK has not been studied in patients with severe renal impairment CrCl <30 mL/min).

Hepatic Impairment
The safety and efficacy of ROZLYTREK have not been studied in patients with hepatic impairment (see Warnings and Precautions, Special Populations; and Pharmacokinetics, Special Populations and Conditions). No dose adjustment is recommended for patients with mild (total bilirubin ≤ 1.5 times ULN) hepatic impairment.

Ethnicity
No dose adjustment is necessary for patients of different ethnicities (see Pharmacokinetics, Special Populations and Conditions).

4.3 Administration

The recommended dose should be administered orally and can be taken with or without food, swallowed whole, and must not be opened or dissolved.

4.4 Missed Dose

If a planned dose of ROZLYTREK is missed, patients can make up that dose unless the next dose is due within 12 hours. If vomiting occurs immediately after taking a dose of ROZLYTREK, patients may repeat that dose.

5 OVERDOSAGE

There is no experience with overdose in clinical trials with ROZLYTREK. Patients who experience overdose should be closely supervised and supportive care instituted. There are no known antidotes for ROZLYTREK.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Oral	Capsule, 100 mg and 200 mg	Colloidal silicon dioxide, crospovidone, hypromellose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, and tartaric acid. The 100 mg capsule shell contains hypromellose, titanium dioxide, and yellow iron oxide. The 200 mg capsule shell contains FD&C yellow #6, hypromellose, and titanium dioxide. The printing ink contains FD&C blue #2 aluminum lake, propylene glycol, shellac, and strong ammonia solution.

ROZLYTREK capsules are supplied as follows:

- 100 mg – bottle containing 30 yellow opaque hard-shell capsules
- 200 mg – bottle containing 90 orange opaque hard-shell capsules

NOC/c 7 WARNINGS AND PRECAUTIONS

Cardiovascular

Congestive Heart Failure

Congestive heart failure (CHF) has been reported across clinical trials with ROZLYTREK (see Table 4 in Adverse Reactions). These reactions were observed in patients with or without a history of cardiac disease and resolved in some patients upon treatment with diuretics and/or dose reduction/interruption of ROZLYTREK. Clinical trials excluded patients with symptomatic CHF, myocardial infarction, unstable angina, or coronary artery bypass graft within three to six months of study entry.

Assess left ventricular ejection fraction (LVEF) prior to initiation of ROZLYTREK in patients with symptoms or known risk factors for CHF. Patients receiving ROZLYTREK should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or edema, should be evaluated and treated as clinically appropriate. For patients with new onset or worsening CHF, withhold ROZLYTREK, institute appropriate medical management and reassess LVEF.

Based on the severity of CHF or worsening LVEF, resume ROZLYTREK treatment at a reduced dose upon recovery to baseline or permanently discontinue ROZYLTREK (see Table 2 in Dosage and Administration).

QTc Interval Prolongation

QT interval prolongation has been observed in patients treated with ROZLYTREK in clinical trials (see Adverse Reactions). Across the clinical trials, 10/355 (2.8%) patients with at least one post-baseline ECG assessment experienced a QTc interval increase over baseline of greater than 60 ms and 6/355 (1.7%) patients had a QTc interval >500 ms. In non-clinical studies, ROZLYTREK caused QT/QTc interval prolongation and had an inhibitory effect on hERG tail currents (See Non-Clinical Toxicology, Safety Pharmacology).

Use of ROZLYTREK should be avoided in patients with congenital long QT syndrome and in patients taking medications that are known to prolong QT interval. Assessment of ECG at baseline and periodic monitoring of ECGs and electrolytes are recommended, adjusting frequency based on risk factors such as congestive heart failure, electrolyte abnormalities, or concomitant medications known to prolong QT interval.

Based on the severity of QTc prolongation, withhold ROZLYTREK treatment and then resume at same or reduced dose, or permanently discontinue (see Table 2 Dosage and Administration).

Driving and Operating Machinery

ROZLYTREK may influence the ability to drive and use machines. If patients experience cognitive adverse reactions, syncope, blurred vision, or dizziness during treatment with ROZLYTREK, patients should be instructed not to drive or operate machines until the symptoms resolve.

Embryo-Fetal Toxicity
Based on the findings in animal studies, ROZLYTREK may cause fetal harm when administered to a pregnant woman. When administrated to pregnant rats, ROZLYTREK caused maternal toxicity and fetal malformations at exposures 2.7 -fold the human exposure by AUC at the recommended dose (see Non-Clinical Toxicology).

Female patients receiving ROZLYTREK should be advised of the potential harm to the fetus. Female patients of reproductive potential, must use highly effective contraceptive methods during treatment and for 5 weeks following the last dose of ROZLYTREK (see Special Populations).

Endocrine and Metabolism
Hyperuricemia
Amongst the 355 patients who received ROZLYTREK across clinical trials, 9% of patients experienced hyperuricemia as an adverse event. Grade 4 events were reported in 1.7% of patients, including one patient who died of tumour lysis syndrome. In all 32 patients with an event of hyperuricemia, 6% required dose reduction, 6% required dose interruption and 34% required interventions to reduce uric acid levels (urate lowering drugs).

Assess serum uric acid levels prior to initiating ROZLYTREK and periodically during treatment. Monitor for signs and symptoms of hyperuricemia. Initiate treatment with urate-lowering medications as clinically indicated, and withhold ROZLYTREK treatment for signs and symptoms of hyperuricemia. Based on the severity of hyperuricemia resume ROZLYTREK at same or reduced dose upon improvement in signs and symptoms (see Table 2, Dosage and Administration).

Hepatic/Biliary/Pancreatic
Amongst the 355 patients who received ROZLYTREK across clinical trials, increases in AST of any grade occurred in 44% of patients and increases in ALT of any grade occurred in 38% of patients. Grade 3-4 increases in AST and ALT occurred in 2.7% and 2.9% of patients respectively. Increases in AST or ALT leading to dose reductions or interruption occurred in 0.8% and 0.8% of patients respectively. The median time to onset of increased AST and ALT was 2 weeks.

Monitor liver function tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Based on the severity of hepatotoxicity, withhold ROZLYTREK treatment and resume at same or reduced dose, or permanently discontinue (see Table 2, Dosage and Administration).

Musculoskeletal
Skeletal Fractures
ROZLYTREK increases the risk of fractures. In an expanded safety population review, 5% of adult patients and 23% of pediatric patients experienced fractures. In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in the pediatric patients, all fractures occurred in patients with minimal or no trauma. In both adults and pediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). The median time to fracture was 3.8 months in adults and 4.0 months in pediatric patients. ROZLYTREK treatment was interrupted in 41% of adults and 43% of pediatric patients due to fractures. No patients discontinued ROZLYTREK due to fractures.

There are no data on the effects of ROZLYTREK on healing fractures or on the risk of future fractures.

Patients with signs and symptoms of fractures should be promptly evaluated. ROZYLTREK is not recommended for use in pediatric patients under the age of 18; Health Canada has not authorized an indication for pediatric use.

Neurologic

Central Nervous System Effects

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with ROZLYTREK (see Adverse Reactions for description of events).

Additionally, a broad spectrum of other central nervous system (CNS) adverse reactions were reported. Amongst the 355 patients receiving entrectinib across clinical trials, 10% experienced mood disorders (depression, anxiety and agitation), 38% experienced dizziness, and 14% experienced sleep disturbances (predominantly insomnia).

The incidence of CNS adverse reactions was similar in patients with or without CNS metastases; however, the incidence of dizziness (38% vs 31%), headache (21% vs 13%), paresthesia (20% vs 6%), balance disorder (13% vs 4%), and confusional state (11% vs 2%) appeared to be increased in patients with CNS metastases who had received prior CNS irradiation (N = 90) compared to those who did not (N = 48).

Patients should be monitored for signs of cognitive changes or other CNS events. Based on the severity, ROZLYTREK treatment should be withheld or permanently discontinued (see Table 2 in Dosage and Administration).

Patients should be counseled on the potential for cognitive changes with ROZLYTREK treatment. If patients experience cognitive changes, they should be instructed not to drive or operate machines until symptoms resolve.

Syncope

Syncope events were reported across clinical trials with ROZLYTREK (see Adverse Reactions). In some patients, syncope was reported with concurrent hypotension, dehydration, or QT prolongation and in other patients no other concurrent related conditions were reported. Patients experiencing syncope should be evaluated and ROZLYTREK treatment should be withheld until recovered, then resumed at reduced dose (see Table 2, Dosage and Administration).

Ophthalmologic

Among the 355 patients who received ROZLYTREK across clinical trials, vision changes occurred in 21% of patients, including Grade 1 (82%), Grade 2 (14%) and Grade 3 (4.1%) (see Adverse Reactions). Vision disorders occurring in $\geq$ 1% included blurred vision (8.7%), photophobia (5.1%), diplopia (3.1%), visual impairment (2%), photopsia (1.1%), cataract (1.1%), and vitreous floaters (1.1%).

Visual disorders have been reported with Anaplastic Lymphoma Kinase (*ALK*) receptor tyrosine kinase inhibitors and entrectinib is reported to inhibit the *ALK* receptor tyrosine kinase.

Patients should be counseled on the potential for visual changes with ROZLYTREK treatment. If patients experience symptoms of vision disorders, they should be instructed not to drive or use machines until symptoms resolve.

For patients with new visual changes, consider an ophthalmological evaluation. Based on the severity of visual changes, withhold ROZLYTREK or modify treatment dosage (see Table 2, Dosage and Administration).

Sexual Health

Pregnancy testing

Women of childbearing potential should not become pregnant while on treatment and should not be pregnant at the beginning of treatment. Female patients of reproductive potential should have medically supervised pregnancy testing prior to initiating ROZLYTREK therapy.

Contraception

Female patients of reproductive potential, must use highly effective contraceptive methods during treatment and for 5 weeks following the last dose of ROZLYTREK (see Non-Clinical Toxicology).

Based on the potential for genotoxicity and risk of teratogenicity, male patients with female partners of child-bearing potential must use highly effective contraceptive methods during treatment and for 3 months following the last dose of ROZLYTREK (see Non-Clinical Toxicology).

Fertility

Dedicated fertility studies were not conducted with entrectinib. Dose-dependent reductions in prostate weight were observed in male dogs (See non-clinical toxicology).

7.1 Special Populations

7.1.1 Pregnant Women

Female patients of reproductive potential must be advised to avoid pregnancy while receiving ROZLYTREK (see Warnings and Precautions). There is no available data on the use of ROZLYTREK in pregnant women. Based on animal studies with entrectinib (see Non-Clinical Toxicology) and its mechanism of action, ROZLYTREK may cause fetal harm when administered to a pregnant woman. Patients receiving ROZLYTREK should be advised of the potential harm to the fetus. Female patients should be advised to contact their healthcare professional, should pregnancy occur.

7.1.2 Breast-feeding

It is not known whether entrectinib or its metabolites are excreted in human breast milk. No studies have been conducted to assess the effects of ROZLYTREK on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, mothers should be advised to discontinue breast-feeding during treatment with ROZLYTREK and for 14 days after the final dose.

7.1.3 Pediatrics

Based on limited data submitted and reviewed by Health Canada, the safety of ROZLYTREK in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

ROZLYTREK has been studied in children, adolescents, and young adults. ROZLYTREK was associated with a higher risk of skeletal fractures in the pediatric population compared to adults (see Musculoskeletal section above). Population pharmacokinetic data demonstrate similar drug exposure in adults and pediatric patients (see Pharmacokinetics, Special Populations and Conditions).

7.1.4 Geriatrics

No differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

7.1.5 Renal Impairment

The safety and efficacy of ROZLYTREK in patients with severe renal impairment have not been studied

7.1.6 Hepatic Impairment

The safety and efficacy of ROZLYTREK in patients with hepatic impairment have not been studied. No dose adjustment is recommended for patients with mild (total bilirubin ≤ 1.5 times ULN) hepatic impairment.

NOC/c

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

For the clinical development program of ROZLYTREK, a total of 355 patients, including 16 pediatric and young adult patients, have received ROZLYTREK in four clinical trials (ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG). The safety of ROZLYTREK was evaluated as integrated analyses of these four ongoing clinical trials. The median duration of exposure to ROZLYTREK was 5.5 months.

In this safety population, the most common tumours were lung (56%), sarcoma (8%), and colon (5%). *ROS1* gene fusions were present in 42% and *NTRK* gene fusions were present in 20%. Most patients (75%) received ROZLYTREK 600 mg orally once daily. The doses ranged from 100 mg/m^2 to 1600 mg/m^2 once daily in adults and 250mg/m^2 to 750 mg/m^2 once daily in pediatric patients. Health Canada has not authorized an indication for pediatric use.

Grade 3-4 adverse reactions occurred in 60% of patients; the most common (≥2%) were lung infection (5%), increased weight (7%), dyspnea (6%), fatigue/asthenia (5%), cognitive disorders (4.5%), syncope (2.5%), pulmonary emboli (3.4%), hypoxia (3.4%), pleural effusion (3.1%), hypotension (2.8%), diarrhea (2%), and urinary tract infection (2.5%).

Fatal events included dyspnea (0.6%), pneumonia (0.6%), sepsis (0.6%), completed suicide (0.3%), large intestine perforation (0.3%), and tumour lysis syndrome (0.3%).

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received ROZLYTREK. The most frequent adverse reaction (<1% each) that resulted in permanent discontinuation were pneumonia, cardio-respiratory arrest, dyspnea, and fatigue.

8.2 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.

Table 4 summarizes the adverse drug reactions (ADRs) occurring in patients treated with ROZLYTREK. Adverse drug reactions from clinical trials are listed by MedDRA system organ class.

Table 4: Summary of Adverse Drug Reactions (>10% for All Grades) Occurring in Patients Treated with ROZLYTREK in Clinical Trials (Integrated Safety Population)

System Organ Class Adverse Reaction	ROZLYTREK N=355	
	All Grades n (%)	Grade 3 – 4 n (%)
General Disorders and Administration Site Conditions		
Fatigue[12]	170 (47.9)	19 (5.4)
Edema[6]	141 (39.7)	4 (1.1)
Pain[7]	100 (28.2)	7 (2.0)
Pyrexia	76 (21.4)	3 (0.8)
Gastrointestinal Disorders		
Constipation	163 (45.9)	2 (0.6)
Diarrhea	123 (34.6)	7 (2.0)
Nausea	122 (34.4)	1 (0.3)
Vomiting	86 (24.2)	3 (0.8)
Abdominal pain	45 (12.7)	2 (0.6)
Dysphagia	35 (9.9)	1 (0.3)
Nervous System Disorders		
Dysgeusia	155 (43.7)	1 (0.3)
Dizziness[5]	136 (38.3)	3 (0.8)
Dysesthesia[3]	103 (29.0)	1 (0.3)
Cognitive Disorders[1]	92 (25.9)	16 (4.5)

System Organ Class Adverse Reaction	ROZLYTREK N=355	
	All Grades n (%)	Grade 3 – 4 n (%)
Peripheral Sensory Neuropathy[2]	63 (17.7)	4 (1.1)
Headache	63 (17.7)	1 (0.3)
Ataxia[4]	59 (16.6)	3 (0.8)
Sleep Disorders[14]	51 (14.4)	2 (0.6)
Mood Disorders[15]	36 (10.1)	2 (0.6)
Respiratory Disorders		
Dyspnea	106 (29.9)	21 (5.9)
Cough	85 (23.9)	1 (0.3)
Blood Disorders		
Anemia	99 (27.9)	38 (10.7)
Neutropenia[9]	43 (12.1)	18 (5.1)
Metabolism and Nutritional Disorders		
Weight increased	88 (24.8)	23 (6.5)
Decreased appetite	46 (13.0)	1 (0.3)
Dehydration	36 (10.1)	4 (1.1)
Renal and urinary disorders		
Blood creatinine increased	82 (23.1)	3 (0.8)
Musculoskeletal Disorders		
Arthralgia	75 (21.1)	2 (0.6)
Myalgia	73 (20.6)	3 (0.8)
Muscular weakness	43 (12.1)	3 (0.8)
Hepatobiliary Disorders		
AST increased	57 (16.1)	12 (3.4)

System Organ Class Adverse Reaction	ROZLYTREK N=355	
	All Grades n (%)	Grade 3 – 4 n (%)
ALT increased	50 (14.1)	11 (3.1)
Infections and Infestations		
Lung Infection[8]	47 (13.2)	18 (5.1)
Urinary tract infection	45 (12.7)	8 (2.3)
Eye Disorders		
Visual disorders[11]	74 (20.8%)	3 (0.8%)
Skin and Subcutaneous Tissue Disorders		
Rash[10]	40 (11.3)	3 (0.8)
Vascular Disorders		
Hypotension[13]	63 (17.7)	10 (2.8)

ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
[1] Includes preferred terms: cognitive disorder, confusional state, disturbance in attention, memory impairment, amnesia, mental status changes, hallucination, delirium, 'hallucination visual', and mental disorder.
[2] Includes the preferred terms: neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy
[3] Includes the preferred terms: paresthesia, hyperesthesia, hypoesthesia, dysesthesia
[4] Includes the preferred terms: ataxia, balance disorder, gait disturbances
[5] Includes the preferred terms: dizziness, vertigo, dizziness postural
[6] Includes the preferred terms: face edema, fluid retention, generalized edema, localized edema, edema, edema peripheral, peripheral swelling
[7] Includes the preferred terms: back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity
[8] Includes the preferred terms: bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection
[9] Includes the preferred terms: neutropenia, neutrophil count decreased
[10] Includes the preferred terms: rash, rash maculopapular, rash pruritic, rash erythematous, rash papular
[11] Includes the preferred terms: blindness, cataract, cortical cataract, corneal erosion, diplopia, eye disorder, photophobia, photopsia, retinal hemorrhage, vision blurred, visual impairment, vitreous adhesions, vitreous detachment, vitreous floaters
[12] Includes the preferred terms: fatigue, asthenia
[13] Includes the preferred terms: hypotension, orthostatic hypotension
[14] Includes the preferred terms: insomnia, somnolence, hypersomnia, sleep disorder
[15] Includes the preferred terms: anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation

8.3 Less Common Clinical Trial Adverse Reactions

Adverse drug reactions occurring in less than 10% of patients include:

Cardiac Disorders: congestive heart failure* (3.4%), and electrocardiogram QT prolongation (2.0%)

*Includes the preferred terms: acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased, pulmonary edema.

Gastrointestinal Disorders: dysphagia (9.9%)

Metabolism and Nutrition Disorders: Hyperuricemia (9.0%)

Musculoskeletal Disorders: bone fractures* (5% in adults; 23% in the pediatric population)
*Includes the preferred terms: humerus fracture, foot fracture, ankle fracture, femoral neck fracture, stress fracture, fibula fracture, fracture, rib fracture, spinal fracture, wrist fracture, femur fracture, pathological fracture.

Nervous System Disorders: syncope (3.9%); cognitive disorders

Cognitive Disorders
A variety of cognitive symptoms were reported across clinical trials. These included events reported as cognitive disorders (7.9%), confusional state (7.3%), disturbance in attention (4.8%), memory impairment (3.7%), amnesia (2.5%), mental status changes (1.7%), hallucination (1.1%), delirium (0.8%), hallucination visual (0.3%), and mental disorder (0.3%). Grade 3 events were reported in 4.5% of patients. In the pediatric population, 6.3% (1/16) pediatric patients experienced disturbance in attention of Grade 1 severity. Patients who had brain metastases at baseline had a higher frequency of these events (39%) compared to those without brain metastases (24.9%).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The following table provides treatment-emergent shifts from baseline in laboratory abnormalities occurring in patients treated with ROZLYTREK across the four clinical trials.

Table 5: Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Treated with ROZLYTREK in Clinical Trials (Integrated Safety Population)

Laboratory Abnormality	ROZLYTREK NCI CTCAE Grade	
	All Grades (%)[1]	Grade 3-4 (%)[1]
Hematology		
Anemia	67	9
Lymphopenia	40	12
Neutropenia	28	7
Chemistry		
Increased creatinine[2]	73	2.1
Hyperuricemia	52	10
Increased AST	44	2.7
Increased ALT	38	2.9
Hypernatremia	35	0.9
Hypocalcemia	34	1.8
Hypophosphatemia	30	7
Increased lipase	28	10
Hypoalbuminemia	28	2.9
Increased amylase	26	5.4
Hyperkalemia	25	1.5
Increased alkaline phosphatase	25	0.9
Hyperglycemia[3]	NE[3]	3.8

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 111 to 346 patients.
[2] Based on NCI CTCAE v5.0
[3] NE = Not evaluable. Grade 1 and 2 could not be determined per NCI CTCAE v5.0, as fasting glucose values were not collected.

8.5 Post-Market Adverse Reactions

Not Applicable.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Table 6: Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Drugs that may increase entrectinib plasma concentrations			
CYP3A inhibitors (Strong and moderate, including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole)	CT	Co-administration of a single oral dose of entrectinib with multiple oral doses of itraconazole, a strong CYP3A4 inhibitor, increased systemic exposure of entrectinib by 500%. GMR with/without itraconazole for AUC_{inf} (90% CI) was 604% (454%, 804%) and C_{max} (90% CI) was 173% (137%, 218%).	Co-administration of strong and moderate CYP3A inhibitors with ROZLYTREK should be avoided or limited to 14 days. If concurrent use is unavoidable, dose adjustment of ROZLYTREK is required (see Dosage and Administration).
Drugs that may decrease entrectinib plasma concentrations			
CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin)	CT	Co-administration of multiple oral doses of rifampin, a strong CYP3A inducer, with a single oral dose of entrectinib reduced systemic exposure of entrectinib by 77%. GMR with/without rifampin for AUC_{inf} (90% CI) was 23.3% (18.4%, 29.5%) and C_{max} (90% CI) was 44.4% (35.3%, 55.9%).	Co-administration of ROZLYTREK with CYP3A inducers should be avoided (see Dosage and Administration).
Effect of entrectinib on CYP substrates			
CYP3A4 substrates (e.g., astemizole, cisapride, cyclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus),	CT	Co-administration of multiple doses of entrectinib and midazolam, a sensitive CYP3A substrate, increased systemic exposure of midazolam by approximately 50% indicating a weak inhibitory effect of entrectinib on the metabolism of midazolam (GMR with/without entrectinib for AUC_{inf} (90% CI) was 150% (129%, 173%)).	No dose adjustment is required when ROZLYTREK is co-administered with CYP3A substrates.

Effect of entrectinib on transporters			
P-gp substrates (e.g. digoxin, topotecan, sirolimus, everolimus, nilotinib, lapatinib)	CT	Co-administration of a single oral dose of entrectinib with a sensitive P-gp substrate, digoxin, increased digoxin C_{max} by approximately 28% and overall exposure by approximately 18% (GMR with/without entrectinib for C_{max} (90% CI) was 128% (98.2%, 167%) and AUC_{inf} (90% CI) was 118% (106%, 132%)). The renal clearance of digoxin was similar between treatments of digoxin alone and digoxin co-administered with entrectinib, indicating minimal effect of entrectinib on renal clearance of digoxin. These results indicate that entrectinib is a weak P-gp inhibitor and that no clinically significant interaction exists between digoxin, as a P-gp substrate, and entrectinib.	No dose adjustment is required when ROZLYTREK is co-administered with P-gp substrates.
Gastric pH elevating medications			
Medicinal products that increase gastric pH (e.g. H2 receptor antagonists or antacids)	CT	Administration of entrectinib with lansoprazole (a proton pump inhibitor (PPI)), resulted in a 25% decrease in entrectinib systemic exposure which is not clinically relevant. GMR with/without lansoprazole for AUC_{inf} (90%CI) was 74.5% (64.7%, 85.9%) and C_{max} (90% CI) was 76.5% (67.6%, 86.6%).	No dose adjustments are required when ROZLYTREK is co-administered with PPIs or other drugs that raise gastric pH.

CT = Clinical Trial

Drugs that Prolong QT Interval

QTc interval prolongation has been reported in 2.8% of patients treated with ROZLYTREK. The concomitant administration of ROZLYTREK with other medicinal products known to prolong the QT interval or induce Torsade de Pointes should be avoided (see Warnings and Precautions, Cardiovascular, QTc Interval Prolongation).

Effects of entrectinib on Other Drugs

CYP substrates
Based on the *in vitro* studies in human liver microsomes, entrectinib exhibits inhibitory potential toward CYP3A.

In vitro studies indicate that entrectinib and its major active metabolite, M5, do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

BCRP substrates
As with P-gp, a mild inhibition of BCRP was observed in *in vitro* studies. Given that no clinically

significant interaction was observed with the P-gp substrate digoxin, an interaction with BCRP is not predicted. No dose adjustment is required when ROZLYTREK is co-administered with BCRP substrates.

Other transporter substrates
In vitro data indicate that entrectinib has weak inhibitory potential toward organic anion-transporting polypeptide (OATP) 1B1 and multidrug and toxin extrusion protein 1 (MATE1).

Oral Contraceptive
Physiologically-based pharmacokinetic simulation of the effects of co-administration of multiple oral doses of entrectinib with ethinyl estradiol, an oral contraceptive, predicted no drug-drug interaction. GMR with/without entrectinib for AUC_{inf} (90% CI) of 112% (111%, 113%) and C_{max} (90% CI) was 112% (111%, 113%).

Therefore ROZLYTREK can be co-administered with an oral contraceptive.

Effects of Other Drugs on entrectinib

Based on *in vitro* data, CYP3A4 is the predominant enzyme mediating the metabolism of entrectinib and formation of its major active metabolite M5.

Effect of transporters on Entrectinib disposition
Entrectinib is a weak P-gp substrate. M5 is a P-gp substrate.

Entrectinib is not a substrate of BCRP but M5 is a substrate of BCRP. Entrectinib and M5 are not substrates of OATP1B1 or OATP1B3.

9.2 Drug-Food Interactions

Entrectinib can be administered with or without food (see ACTION AND CLINICAL PHARMACOLOGY: 10.3 Pharmacokinetics – Absorption.) Grapefruit or grapefruit juice with ROZLYTREK should be avoided.

9.3 Drug-Herb Interactions

St. John's Wort (hypericum perforatum) is a strong CYP3A inducer. Co-administration of St. John's Wort with ROZLYTREK should be avoided (see Drug-Drug Interactions).

9.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.5 Drug-Lifestyle Interactions

ROZLYTREK may influence the ability to drive and operate machines (see Warnings and Precautions).

10 ACTION AND CLINICAL PHARMACOLOGY

NOC/c

10.1 Mechanism of Action

Entrectinib is a potent inhibitor of receptor tyrosine kinases TRKA, TRKB, and TRKC (encoded by the neurotrophic tyrosine receptor kinase [*NTRK*] genes *NTRK1*, *NTRK2,* and *NTRK3*, respectively), proto-oncogene tyrosine-protein kinase ROS (*ROS1*; encoded by the gene *ROS1*), and anaplastic lymphoma kinase (*ALK*; encoded by the gene *ALK*) with IC_{50} values ranging from 0.1 to 2 nM. Entrectinib also inhibits JAK2 with an IC_{50} value of 5.4 nM. The major active metabolite of entrectinib, M5, showed similar *in vitro* potency and activity.

Fusion proteins that include TRK, *ROS1* or *ALK* kinase domains drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Entrectinib potently inhibits the TRK kinases, *ROS1*, and *ALK*, leading to inhibition of downstream signaling pathways, cell proliferation and induction of tumour cell apoptosis. Entrectinib demonstrates potent inhibition of cancer cell lines derived from multiple tumour types harboring *NTRK*, *ROS1*, and *ALK* fusion genes. Entrectinib has anti-tumour potency in *NTRK* and *ROS1* fusion-driven tumour models, driving tumour regressions across cell-line and patient-derived xenograft models.

It has demonstrated potent anti-tumour activity in three *NTRK1*-driven intracranial tumour models, including two high grade glioma mouse models. These data are consistent with entrectinib dosing resulting in sufficient brain exposure achieving target pharmacological activities at steady-state and at clinically relevant systemic exposures.

Prior treatments with other drugs that inhibit the same kinases may confer resistance to entrectinib. Point mutations in the *NTRK1* (G595R, G667C) and *NTRK3* (G623R, G623E and G623K) kinase domains have been identified with clinically acquired resistance to entrectinib.

10.2 Pharmacodynamics

Cardiac Electrophysiology
An ECG sub-study was conducted in patients who received ROZLYTREK 600 mg once daily. Entrectinib exposure-dependent trends in change from baseline in QTcF were not apparent in the analysis of ECG data, which included 107 patients with concentrations at dates/times matching the QT assessment.

10.3 Pharmacokinetics

The pharmacokinetic parameters for entrectinib and its major active metabolite (M5) have been characterized in patients with locally advanced/metastatic tumours, including patients with *NTRK*-positive solid tumours and *ROS1*-positive NSCLC from study STARTRK-1 (see Table 7).

Table 7: Pharmacokinetic Parameters for Entrectinib and Metabolite M5

Parameter	Entrectinib Mean* (% CV)	M5 Mean* (% CV)
AUC_{D1} (nM*h)	31800 (48%)	10200 (82%)
AUC_{SS} (nM*h)	48000 (77%)	24000 (97%)
C_{maxD1} (nM)	2250 (58%)	622 (79%)
C_{maxss} (nM)	3130 (80%)	1250 (90%)
$R_{acc(AUC)}$	1.55 (49%)	2.84 (93%)
*Geometric mean		

Absorption: Following a single 600 mg oral administration of ROZLYTREK to patients with locally advanced or metastatic cancer, entrectinib was rapidly absorbed reaching time-to-maximum plasma concentration (T_{max}) after approximately 4 - 6 hours. Based on population pharmacokinetic analysis, steady-state was achieved within 5 days for entrectinib with 600 mg once daily dosing.

The estimated absolute bioavailability of entrectinib based on physiologically based pharmacokinetic (PBPK) modeling was 55%.

Co-administration of a high-fat (approximately 50% of total caloric content), high-calorie (approximately 800 to 1000 calories) meal with a single dose of entrectinib in healthy, adult volunteers delayed T_{max} by approximately 2 hours without significantly altering C_{max}. There was no significant impact of a high-fat, high-calorie meal on entrectinib exposure (AUCT) when compared to administrations under fasting conditions. Entrectinib can may be administered with or without food (see Dosage and Administration).

Distribution: Entrectinib and its major active metabolite M5 are highly bound to human plasma proteins independent of drug concentrations. In human plasma, entrectinib and M5 had similar protein binding with >99% bound *in vitro*.

After a single oral dose of [^{14}C]-labeled entrectinib, the geometric mean volume of distribution (Vz/F) was 860 L, suggesting extensive distribution into tissues. Population pharmacokinetic analysis estimated volume of distribution of 551 L and 81.1 L for entrectinib and M5, respectively.

Entrectinib is a CNS penetrant molecule that showed brain-to-plasma concentration ratios of 0.4-2.2 in multiple animal species (mice, rats, and dogs).

Metabolism: Entrectinib is metabolized predominantly by CYP3A4 (~76%). Minor contributions from several other CYPs and UGT1A4 were estimated at <25% in total. The active metabolite M5 (formed by CYP3A4) and the direct N-glucuronide conjugate, M11 (formed by UGT1A4), are the two major circulating metabolites identified.

Elimination: Following administration of a single dose of [^{14}C]-labeled entrectinib administered orally to healthy subjects, the majority of radioactivity was excreted in feces (82.9%) with minimal excretion in urine (3.06%). In feces, 35.7% and 22.1% of the dose was excreted as unchanged entrectinib and M5, respectively, indicating hepatic clearance is the major route of elimination.

Entrectinib and M5 account for approximately 73% of radioactivity in systemic circulation at C_{max}, and approximately half of total radioactivity AUC_{INF}.

Population PK analysis estimated a CL/F of 19.6 L/h and 52.4 L/h for entrectinib and M5, respectively. The elimination half-lives of entrectinib and M5 were estimated to be 20 and 40 hours, respectively.

Special Populations and Conditions

Pediatrics: Non-compartmental analysis and population pharmacokinetic modeling approaches suggested that the pharmacokinetics of entrectinib and M5 were comparable in adults and children allowing extrapolation of data in adults to pediatric patients.

Data obtained from population pharmacokinetic analyses suggest that a dose of 300 mg/m^2 of ROZLYTREK once daily in pediatric patients results in a similar systemic exposure attained in adults treated with 600 mg of ROZLYTREK, once daily. Population pharmacokinetic analysis data support dosing of pediatric patients with BSA ≥ 1.51 m^2 with 600 mg of ROZLYTREK once daily. A pediatric indication has not been granted by Health Canada for ROZLYTREK.

Geriatrics: No differences in entrectinib exposure were noted in patients older than 65 years and younger adults based on pharmacokinetic analysis.

Ethnic origin: Following a single oral dose of ROZLYTREK in Japanese and Caucasian healthy volunteers, no clinically relevant differences in the exposure of ROZLYTREK were observed. Based on population pharmacokinetics analysis, there was no relationship between systemic exposure of entrectinib and race/ethinicity (Asian, Japanese, white and other ethnicities). No dose adjustment is required for patients of different race/ethnicities (see Dosage and Administration).

Hepatic Insufficiency: As elimination of entrectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of entrectinib and/or its major active metabolite M5. Limited clinical data is available in patients with hepatic impairment and a dedicated pharmacokinetic study in patients with hepatic impairment has not been conducted. No dose adjustment is recommended for patients with mild (total bilirubin ≤ 1.5 times ULN) hepatic impairment. ROZLYTREK has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) and severe (total bilirubin > 3 times ULN) hepatic impairment.

Renal Insufficiency: Negligible amounts of entrectinib and the active metabolite M5 are excreted unchanged in urine (~3 % of the dose) indicating renal clearance plays a minor role in the elimination of entrectinib. Population pharmacokinetic data obtained in patients with mild and moderate impairment show that pharmacokinetics of entrectinib are not significantly affected in renal impairment. No formal pharmacokinetic study has been conducted and no population pharmacokinetic data was collected in patients with severe renal impairment.

10.4 Published Reports

Published reports of individuals with congenital mutations in TRK pathway proteins suggest that decreases in TRK-mediated signaling are correlated with obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-30°C).

This medicine should not be used after the expiry date (EXP) shown on the pack.

12 SPECIAL HANDLING INSTRUCTIONS

Disposal of Unused/Expired Medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

ROZLYTREK, indicated for:

- the treatment of adult patients with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, and with no satisfactory treatment options

has been issued marketing authorization with conditions, pending the results of new information to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ROZLYTREK please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

13 PHARMACEUTICAL INFORMATION

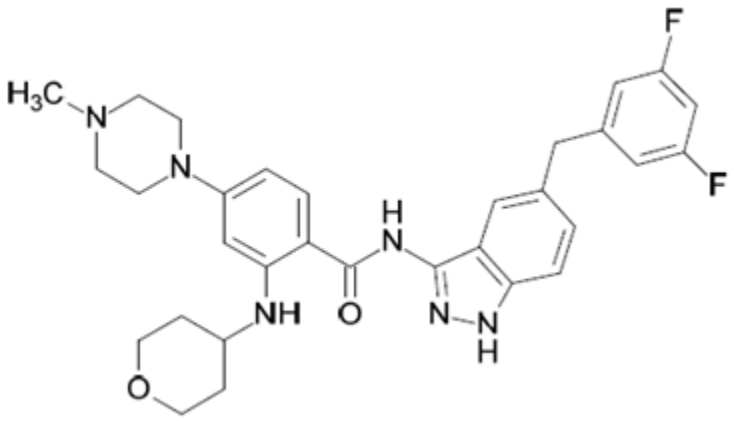
Drug Substance

Proper/Common name: entrectinib

Chemical name: N-{5-[(3,5-difluorophenyl)methyl]-1H-indazol-3-yl}-4-(4-methylpiperazin-1-yl)-2-[(oxan-4-yl)amino]benzamide

Molecular formula and molecular mass: $C_{31}H_{34}F_2N_6O_2$, 560.64 g/mol

Structural formula:



Physicochemical properties: Entrectinib is a white to off-white or pale pink powder or powder with lumps. The solubility of entrectinib in aqueous media has a pronounced dependence on the pH value. At high pH values, entrectinib has a solubility of about 0.004 mg/mL. With decreasing pH values (pH = 1.2), the solubility increases up to > 40 mg/mL. Entrectinib is defined as poorly soluble, as the highest dose strength (200 mg) is not soluble in less than 250 mL water over the entire pH range of 1.2-6.8.

14 CLINICAL TRIALS

NOC/c

14.1 Trial Design and Study Demographics

Three open-label clinical trials in patients with advanced cancer contributed to a pre-specified integrated efficacy analysis evaluating ROZLYTREK in the treatment of extracranial *NTRK* fusion-positive solid tumours in adult patients ≥ 18 years of age ALKA, n=1; STARTRK-1, n=2; and STARTRK-2, n=51).

Study ALKA was a Phase I single arm, open-label study in adult patients with solid tumours with *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations to determine the maximum tolerated dose. Study STARTRK-1 was a Phase I multi-center single arm, open label study in adult patients with solid tumours with *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations. The study included a dose escalation segment and a dose expansion segment. In the dose expansion segment, patients received 600 mg daily in repeated 4-week cycles and the primary objective was to evaluate the recommended Phase II dose. Study STARTRK-2 is an ongoing multicenter, international Phase II single-arm basket study in adult patients with solid tumours with *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangements. Patients received 600 mg ROZLYTREK once daily in 4-week cycles.

The primary efficacy outcome measures in the integrated analyses were objective response rate (ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Secondary efficacy outcome measures included intracranial (IC) ORR and IC-DOR (also evaluated by BICR using RECIST v1.1) in patients presenting with measurable CNS metastases at baseline.

The efficacy evaluable analysis set comprised a total of 54 adult patients with confirmed *NTRK* fusion-positive extracranial solid tumours treated with ROZLYTREK, not previously treated with a TRK inhibitor, presenting with measurable disease at baseline as assessed by investigator, and with ≥ 6 months of follow up. *NTRK* fusion-positive status was determined by a validated nucleic acid-based test performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited laboratory, prior to enrollment in the study. A total of 52 (96%) patients had an *NTRK* gene fusion detected by NGS and 2 (4%) had an *NTRK* gene fusion detected by other nucleic acid-based tests. Eighty-three percent of patients had central laboratory confirmation of *NTRK* gene fusion using an analytically validated NGS test.

The baseline demographic and disease characteristics of the efficacy evaluable population were: 41% males, median age of 57 years (range: 21 to 83 years), 80% white, 13% Asian, and 57% never smoked. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (43%), 1 (46%), or 2 (11%). Most patients (96%) had metastatic disease [most common sites being lung (61%), lymph nodes (56%), and brain (22%)], 4% patients had locally advanced disease, and 37% patients had no prior systemic therapies. The overall median duration of follow-up was 13 months.

14.2 Study Results

Efficacy in Adult Patients

Efficacy results from patients with *NTRK* fusion-positive solid tumours are summarized in Table 8.

Table 8: Overall Efficacy by BICR in Adults with *NTRK* Fusion-Positive Solid Tumours

Efficacy Endpoints	ROZLYTREK N=54
Primary endpoints (BICR-assessed, RECIST 1.1)	
ORR	
Number of CR+PR	31/54
ORR% (95% CI)	57% (43, 71)
Complete Response, n (%)	4 (7%)
Partial Response, n (%)	27 (50%)
DOR [2]*	**N = 31**
Number (%) of patients with events	16/31 (52%)
Median, months (95% CI)	10.4 (7.1, NE)
% duration ≥ 6-months	69%
% duration ≥ 9-months	59%
% duration ≥ 12-months	49%

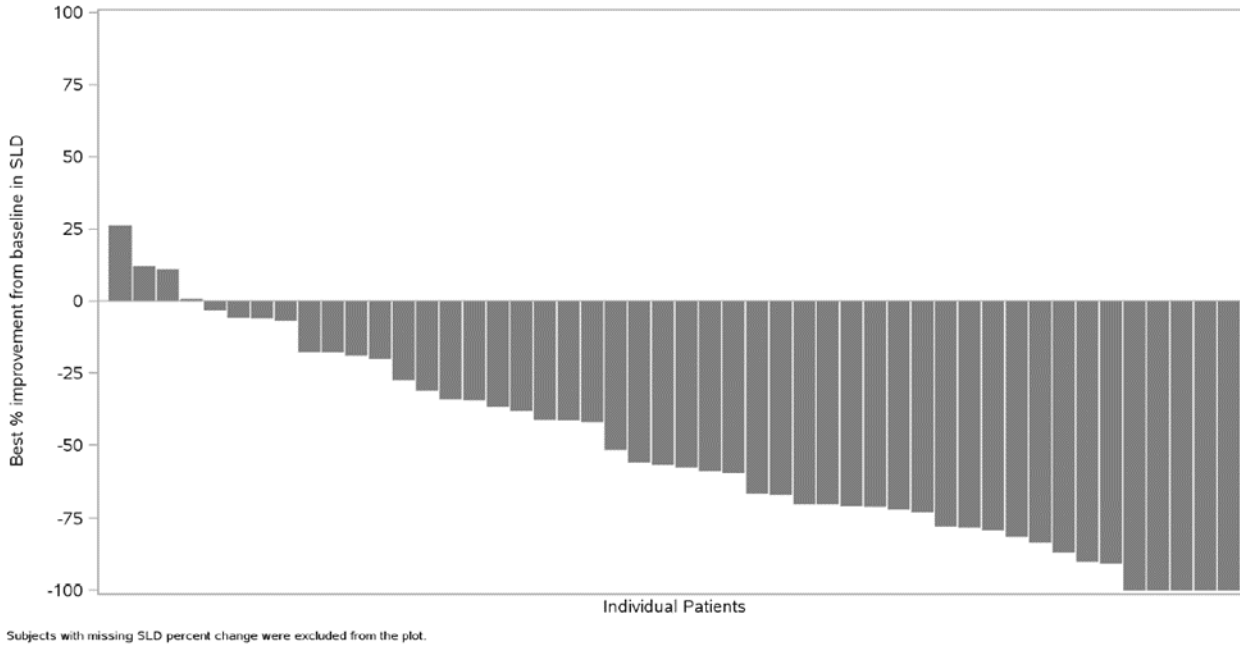
ORR : objective response rate ; CR: complete response; PR: partial response; DOR : duration of response ; NE: not estimable.

[1]Confidence Intervals (CI) calculated using the Clopper-Pearson method.

[2]*Median and percentiles based on Kaplan-Meier estimates, 95% CI for median was computed using the method of Brookmeyer and Crowley.

Shown in Figure 1 is the best percentage change in the sum of target lesions from baseline for individual patients as assessed by BICR according to RECIST 1.1.

Figure 1: Best Percentage Change in the Sum of Target Lesions from Baseline (BICR Assessment) in Adults with *NTRK* Fusion-Positive Solid Tumours



SLD: Sum of Longest Diameter

Objective response rate by tumour type in all efficacy evaluable adult patients with *NTRK* fusion-positive solid tumours is presented in Table 9.

Table 9: Objective Response Rate and Duration of Response (BICR Assessment) by Tumour Type in Adults with *NTRK* Fusion-Positive Solid Tumours

Tumour Type	N	Responders n (%)	95% CI	DOR Range (months)
All	54	31 (57%)	(43, 71)	
Breast cancer All Secretory Non-secretory	 6 4 2	 5 (83%) 4 (100%) 1 (50%)	 (36, 100) (40, 100)	 4.2, 14.8*
Cholangiocarcinoma	1	1 (100%)	NA	9.3
Colorectal cancer	4	1 (25%)	(1, 81)	4.8*
Gynecological cancers	2	1 (50%)	NA	20.3*
Neuroendocrine cancers	3	1 (33%)	NA	5.6*
Non-small cell lung cancer	10	7 (70%)	(35, 93)	1.9*, 20.1*
Pancreatic cancer	3	2 (67%)	NA	7.1, 12.9
Salivary (MASC)	7	6 (86%)	(42, 100)	2.8, 16.5*
Sarcoma	13	6 (46%)	(19, 75)	2.8, 15.1
Thyroid cancer	5	1 (20%)	(1, 72)	7.9
*censored				

MASC: mammary analogue secretory carcinoma
Confidence Intervals (CI) are calculated using the Clopper-Pearson method.

Table 10: Objective Response Rate and Duration of Response (BICR Assessment) by Gene Fusion Partner in Adults with *NTRK* Fusion-Positive Solid Tumours

NTRK Partner	N	Responders n (%)	95% CI	DOR Range (months)
ETV6 - *NTRK3*	25	17 (68%)	(46, 85)	2.8, 20.3*
TPM3 - *NTRK1*	4	2 (50%)	(7, 93)	2.8, 15.1
TPR - *NTRK1*	4	4 (100%)	(40, 100)	5.6, 12.9*
LMNA - *NTRK1*	2	1	NA	4.2
SQSTM1 - *NTRK1*	2	2	NA	3.6, 18.8*
PEAR1 - *NTRK1*	2	0	NA	NA
EML4 - *NTRK3*	2	0	NA	NA
CD74 - *NTRK1*	1	1	NA	10.4
PLEKHA6 - *NTRK1*	1	1	NA	9.3
CDC42BPA - *NTRK1*	1	1	NA	6.8*
EPS15L1 - *NTRK1*	1	1	NA	1.9*
RBPMS - *NTRK3*	1	1	NA	4.6
ERC1 - *NTRK1*	1	0	NA	NA
PDIA3 - *NTRK1*	1	0	NA	NA
TRIM33 - *NTRK1*	1	0	NA	NA
AKAP13 - *NTRK3*	1	0	NA	NA
KIF7 - *NTRK3*	1	0	NA	NA
FAM19A2 - *NTRK3*	1	0	NA	NA
CGN - *NTRK1*	1	0	NA	NA
SQSTM1 - *NTRK2*	1	0	NA	NA

* censored

Confidence Intervals (CI) are calculated using the Clopper-Pearson method.

Intracranial Response

Of the 54 adult patients with *NTRK* fusion-positive solid tumours in the efficacy evaluable analysis set, 11 patients had CNS metastases at baseline as assessed by BICR, including 7 patients with measurable CNS lesions. Intracranial ORR and DOR (assessed by BICR according to RECIST version 1.1) in this subgroup of patients with measurable CNS lesions at baseline are summarized in Table 11.

Table 11: Intracranial Efficacy in Adults with *NTRK* Fusion-Positive Solid Tumours with CNS Metastases at Baseline by BICR

Secondary Endpoint *(BICR-assessed, RECIST 1.1)*	**CNS Metastases at Baseline (by BICR)** **Measurable disease N=7**
IC-ORR	
Responders	4
IC-ORR% (95% CI)[1]	57% (18, 90)
Complete Response n (%)	1 (14%)
Partial Response n (%)	3 (43%)
IC-DOR	
Number of patients with events (%)	1 (25%)
Median, months (95%)[2]	NE (5, NE)

NE: not estimable.
IC-ORR derived using RECIST 1.1 criteria applied only to CNS lesions.
[1]Confidence Intervals (CI) calculated using the Clopper-Pearson method.
[2]Median based on Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.

Patient Reported Outcomes
Study STARTRK-2 evaluated patient-reported outcomes (PROs) of the treatment impact on functioning and health-related quality of life (HRQoL) based on the EORTC Core Quality of Life Questionnaire (QLQ-C30). A change from baseline of ≥10 points on a 1-100 scale was considered clinically meaningful, with higher scores reflecting better functioning and HRQoL. Cycle 10 was selected as the last time-point providing representative information considering that by then less than 50% of the PRO evaluable population was still in the study.

At baseline, patients reported moderate to high baseline values on HRQoL and functioning scales (Global health status: 70; Role functioning: 67; Physical functioning: 74; Cognitive functioning: 85). Throughout the study (Cycle 2-Cycle 10), 20 to 31% of patients reported clinically meaningful improvement of global health status (QoL), while 25 to 41% reported clinically meaningful worsening. Across the functioning scales, 19 to 48% of patients reported clinically meaningful improvement in role and physical functioning, while 33 to 46% reported clinically meaningful worsening in cognitive functioning.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicity
Entrectinib-related toxicities in repeat dose studies of up to 13-weeks with daily oral gavage administration in adult rats and dogs, and juvenile rats were observed in the CNS (convulsions, abnormal gait, tremors) at ≥ 0.2 times the human exposures by C_{max} at the recommended dose, skin (scabs/sores) and decreased RBC parameters at ≥ 0.1 times the human exposure by AUC at the recommended dose. In adult rats and dogs, effects on liver (increased ALT and hepatocellular necrosis) were observed at ≥ 0.8 times the human exposure by AUC at the recommended dose. In dogs, diarrhea at ≥ 0.1 times the human exposure by AUC at the recommended dose was also observed.

Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of entrectinib.

Genotoxicity
Entrectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay. Entrectinib was not clastogenic in the in vivo micronucleus assay in rats and did not induce DNA-damage in a comet assay in rats. A potential for abnormal chromosome segregation (aneugenicity) has been detected under *in vitro* conditions in cultured human peripheral blood lymphocytes (HPBL) but was not detected in the *in vivo* micronucleus assay in rats.

Reproductive Toxicity
In an embryo-fetal developmental study in rats, maternal toxicity (decreased body weight gain and food consumption) and fetal malformations (including body closure defects and malformations of the vertebrae, limbs, and ribs), were observed at 200 mg/kg/day of entrectinib, which represents approximately 2.7-fold the human exposure by AUC at the recommended dose. Lower fetal weights and reduced skeletal ossification were observed at doses ≥ 12.5 and 50 mg/kg, approximately ≥ 0.2 and ≥ 0. 9 times the human exposure by AUC (48 μM•h) at the recommended dose, respectively.

Impairment of Fertility
Dedicated fertility studies were not conducted with entrectinib. With the exception of dose-dependent decreases in prostate weight in male dogs, there were no effects on male and female reproductive organs observed in general toxicology studies conducted in rats and dogs by daily oral gavage administration, at doses resulting in exposures of up to approximately 3.2-fold the human exposure (AUC) at the 600 mg dose.

Juvenile Toxicity
In a 13-week juvenile rat toxicology study, animals were dosed daily by oral gavage from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Entrectinib was dosed at 4, 8 or 16 mg/kg/day approximately 0.06, 0.14 and 0.18 times the human exposures by AUC at the 600 mg dose. Entrectinib related mortality was observed at 16 mg/kg/day. CNS related toxicity signs included non-sustained convulsions at ≥ 8 mg/kg/day, and abnormal gait, decreased activity and tremors at 16 mg/kg/day. Additional entrectinib-related clinical signs included eyes partly closed, erected fur, dehydration, skin scabs, fur loss or thin fur, and fur staining at all dose levels and hunched posture, pale skin, labored breathing, prostration, low carriage, and increased breathing rate at 16 mg/kg/day. Effects on growth and development were observed in the dosing and recovery phases including decreased body weight gain and delayed sexual maturation at ≥ 4 mg/kg/day, deficits in neurobehavioral assessments including functional observational battery (decreased landing foot splay, grip strength) and learning and memory at ≥ 8 mg/kg/day, and decreased femur length at 16 mg/kg/day.

Safety Pharmacology
In dogs, daily oral gavage administration of entrectinib caused prolongation of QT/QTc interval at ≥ 0.1 times the human exposure by C_{max} at the recommended dose. In an *in vitro* hERG assay in stably transfected HEK293 cells under patch clamp conditions, IKr channel inhibition was observed with an IC_{50}=0.6 μM.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr ROZLYTREK®
entrectinib capsules

Read this carefully before you start taking **ROZLYTREK** 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 **ROZLYTREK**.

What is ROZLYTREK used for?

For the following indication ROZLYTREK 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 studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

ROZLYTREK is used to treat adults with solid tumours that have a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion without a known resistance mutation. ROZLYTREK can treat cancers that have spread to different parts of the body. It is for patients without other treatment options.

To benefit from ROZLYTREK, 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 ROZLYTREK.

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 a 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 a 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.

Serious Warnings and Precautions

- ROZYLTREK may harm your unborn baby.
- ROZYLTREK may cause congestive heart failure. This occurs when your heart muscle does not pump blood as well as it should.

How does ROZLYTREK work?
ROZLYTREK works by blocking the action of enzymes which have a fault in them. This fault is in the *NTRK* genes that make the enzymes. The faulty enzymes encourage the cancer cells to grow. ROZLYTREK may slow down or stop the cancer from growing. It may also help to shrink your cancer.

What are the ingredients in ROZLYTREK?
Medicinal ingredient: entrectinib
Non-medicinal ingredients:
Colloidal silicon dioxide, crospovidone, FD&C blue #2 aluminum lake, hypromellose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, propylene glycol, shellac, strong ammonia solution, tartaric acid, titanium dioxide.

Capsules also contain:
- 100 mg: yellow iron oxide
- 200 mg: FD&C yellow #6

ROZLYTREK comes in the following dosage forms:
Capsule: 100 mg and 200 mg

Do not use ROZLYTREK if:
- You are allergic to any ingredients in this drug or the bottle.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ROZLYTREK. Talk about any health conditions or problems you may have, including if you:
- Have any heart problems, including long QT syndrome. This is a **heart rhythm condition**.
- Have excess uric acid in your blood.
- Have liver or kidney problems.
- Have bone fractures.
- Have nervous system (neurological) problems.
- Have or have had eye or vision problems.

Other warnings you should know about:

- Only a doctor who has experience treating cancer should treat you with this drug.

Female Patients:
- Avoid becoming pregnant while taking ROZLYTREK. It may harm your unborn baby.
- Use highly effective birth control if you can get pregnant while taking ROZLYTREK and for 5 weeks after your last dose.
- Tell your healthcare professional right away if you become pregnant or think you are pregnant during treatment with ROZLYTREK.
- You should not be pregnant at the beginning of treatment with ROZLYTREK. The doctor should do a pregnancy test before you start ROZLYTREK.
- It is not known if ROZLYTREK passes into breast milk. Do not breastfeed during treatment with ROZLYTREK and for 14 days after the final dose. Talk to your healthcare professional about the best way to feed your baby during this time.

Male Patients:
- Use highly effective birth control if your partner can get pregnant while you are on ROZLYTREK and for 3 months after your last dose.

Children less than 18 years of age:
- ROZLYTREK is not recommended for use in children less than 18 years of age. There is a higher risk of bone fractures in children compared to adults when using ROZLYTREK.

Driving and using machines:
- Before you do tasks which require attention wait until you know how you respond to ROZLYTREK. It can cause you to feel faint, dizzy, or tired. It can give you blurred vision, mental status changes, confusion, and hallucinations. Do not drive or operate machines until you feel well.

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

The following may interact with ROZLYTREK:
- Telithromycin – used to treat certain types of bacterial infection
- St. John's Wort (*hypericum perforatum*) – a herbal medicine, used to treat depression
- Ritonavir, saquinavir - used to treat AIDS/HIV infection
- Itraconazole, ketoconazole, posaconazole and voriconazole - used to treat fungal and bacterial infections
- Phenytoin, carbamazepine, phenobarbital - used to treat seizures
- Rifampin, rifabutin – used to treat lung disease
- Grapefruit and grapefruit juice

How to take ROZLYTREK:
- Take exactly as prescribed for you by your healthcare provider. Continue to take ROZLYTREK unless your healthcare provider tells you to stop. Treatment may continue until the cancer gets worse or you get side effects that could prevent treatment continuation.
- Take with or without food.
- Swallow whole. Do not open or dissolve the capsules.
- If you vomit right after taking a dose, you may take the dose again.

Usual dose:
Adults
- Recommended dose: 600 mg once a day.
- Your healthcare professional will monitor your health. Your doctor may interrupt, reduce, or stop your dose. This may occur based on your current health, if you take certain other medications, if your disease gets worse, or if you have too many side effects.

Overdose:

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

Missed Dose:

- If you are less than 12 hours late, take the missed dose as soon as you remember. Take the next dose at your regular time.
- If you are more than 12 hours late, do NOT take the missed dose. Wait until the regular time for your next dose.
- Do not take a double dose to make up for a missed dose.

What are possible side effects from using ROZLYTREK?

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

The most common side effects of ROZLYTREK include:

- tiredness, difficulty sleeping
- constipation, diarrhea, nausea, vomiting, abdominal pain
- change in sense of taste and touch
- swelling
- dizziness, headaches
- abnormal touch sensation
- pain in joints, muscles or nerves
- weakness of muscles
- weight gain, loss of appetite, difficulty swallowing
- cough
- fever
- rash

ROZLYTREK can cause abnormal exam and blood test results. Your doctor will do some tests before and during your treatment. These include checking for heart and 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			
Anemia (reduction in the number of red blood cells): Feel tired, looking pale and you may feel your heart pumping		✓	
Decreased Neutrophils (a kind of white blood cells): Fever, fatigue, mouth ulcer, sore throat, or infections.		✓	
Dehydration (when there is not enough water in the body): Thirst, reduced sweating and urine, dry mouth, dizziness	✓		

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	
Eye problems: blurred vision, loss of vision in eye, double vision, increased sensitivity of the eyes to light, clouding of lens in eye, spots in vision that appear as specks or strings of floating material; spots that move with eye movement.		✓	
Liver Problems and increased liver enzymes: Loss of appetite, feeling sick or being sick, yellow skin, itching or pain in your liver area.		✓	
Lung problems: difficult and painful breathing, shortness of breath, cough, wheezing, fever, stuffy nose, chest pain when you breath or cough		✓	
Nervous System / Cognitive Disorders: feeling confused, mental status change, anxiety, persistent sad mood, decreased attention and awareness. Disorientation, agitation. Having memory problems. See or hear things that are not there (hallucinations).		✓	
Urinary tract infection: blood in urine, pain when you go pee.		✓	
COMMON			
Congestive Heart Failure (heartdoes not pump blood as well as it should): cough, shortness of breath, swelling in your legs, arms, ankles and feet, fluid retention, lack of appetite, rapid or irregular heart beat.			✓
Hypotension (low blood pressure): dizziness, fainting, lightheadedness.		✓	
Hyperuricemia (high levels of uric acid in the blood): severe		✓	

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	
pain in joints, joint stiffness, redness and swelling in joints.			
Syncope (fainting)		✓	
Pulmonary embolism (blood clot in the lung): severe chest pain, coughing up blood, shortness of breath.			✓
Prolongation of QT interval (a heart rhythm condition): Irregular heartbeat, fainting, loss of consciousness, seizures.			✓
NOT COMMON			
Bone fractures (broken bone): Area around break will be painful and swollen, bulge or bump at site of break, broken bone may push through skin.		✓	
Sepsis (serious infection due to bacteria in your blood): 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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:

- Store ROZLYTREK at room temperature (15°C to 30°C).
- Do not use this medicine after the expiry date (EXP) shown on the pack.
- Keep out of reach and sight of children.

If you want more information about ROZLYTREK:

- 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 (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.rochecanada.com, or by calling 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Limited.

Last Revised: February 7, 2020