Drug Monograph

A - Drug Name

entrectinib

COMMON TRADE NAME(S): Rozlytrek®

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B - Mechanism of Action and Pharmacokinetics

Entrectinib is a tyrosine kinase inhibitor targeting TRKA, TRKB, TRKC (encoded by NTRK genes), proto-oncogene tyrosine-protein kinase ROS1, and anaplastic lymphoma kinase (ALK). Fusion proteins that include TRK, ROS1, or ALK kinase domains act as oncogenic drivers to promote hyperactivation of downstream signaling pathways, resulting in unchecked cell proliferation. By potently inhibiting the TRK kinases, ROS1, and ALK, entrectinib inhibits downstream signalling pathways, cell proliferation and induces tumour cell apoptosis.

Absorption	Bioavailability	55%
	Peak plasma levels	4 - 6 hours
	Time to reach steady state	5 days
	Effects with food	Co-administration of a high-fat , high-calorie meal delayed T_{max} by ~ 2 hours without significant impact to C_{max} or AUC.
Distribution	Entrectinib has extensive tissue distribution.	
	PPB	>99% to plasma proteins.
	Cross blood brain barrier?	Yes

Metabolism	Entrectinib is metabolized by CYP3A4 (~76%), other CYPs and UGT1A1.	
	Active metabolites	Yes (major metabolite: M5)
	Inactive metabolites	Yes
Elimination	Feces	83%; 36% as unchanged drug, and 22% as M5
	Urine	3%
	Half-life	Entrectinib: 20 hours; M5: 40 hours

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C - Indications and Status

Health Canada Approvals:

- Solid tumors with NTRK fusion-positive status
- Non-Small Cell Lung Cancer (NSCLC)

(Includes conditional approvals)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following table lists pooled adverse effects that occurred in ≥ 10% of patients who received entrectinib in 4 clinical trials including patients with NTRK gene fusion positive tumors and patients with ROS1 Positive NSCLC. Severe or life-threatening adverse effects from other sources or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (3%)	E D L
	Hypotension (18%)	E
	QT interval prolonged (2%)	E
Dermatological	Rash (11%)	E
Gastrointestinal	Abdominal pain (13%)	E
	Anorexia (13%)	E
	Constipation (46%) (1% severe)	E
	Dehydration (10%)	E
	Diarrhea (35%)	E
	Nausea, vomiting (34%)	E
	Weight gain (25%)	E
General	Edema (40%) (1% severe)	E
	Fatigue (48%)	E
	Fever (21%)	E
Hematological	Myelosuppression ± infection (28%) (including anemia) (11% severe)	E
Hepatobiliary	↑ LFTs (16%)	E D
Metabolic / Endocrine	Hyperuricemia (9%) (2% severe)	E
Musculoskeletal	Fracture (5%)	E D
	Musculoskeletal pain (21%)	E
Nervous System	Ataxia (17%)	E
	Cognitive disturbance (26%) (5% severe)	E D
	Dizziness (38%)	E
	Dysesthesia (29%) (including peripheral neuropathy)	E
	Dysgeusia (44%) (<1% severe)	E
	Headache (18%)	E
	Mood changes (10%)	E D
	Sleep disorder (14%)	E
	Syncope (4%)	E
Ophthalmic	Eye disorders (21%) (<1% severe)	E
Renal	Creatinine increased (23%)	E
Respiratory	Cough, dyspnea (30%)	E

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

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

The most common side effects for entrectinib include fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, vomiting, cough, dyspnea, dysesthesia and myelosuppression.

Congestive heart failure (CHF) has been reported. 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 entrectinib. The median time to onset of heart failure was 2 months (range: 11 days to 12 months). In addition, myocarditis in the absence of CHF was documented in <1% of patients.

Entrectinib increases the **risk of fractures**. In adult patients, some fractures occurred secondary to a fall or other trauma to the affected area. Most fractures occurred in the hip or other lower extremity fractures (e.g., femoral or tibial shaft) within 3.8 months (median time). There are no data on the effects of entrectinib on healing fractures or on the risk of future fractures.

Cognitive disorders, including confusion, memory impairment, and hallucinations, have been reported. Symptoms occurred within 3 months of entrectinib initiation in the majority of patients. Patients who had brain metastases at baseline had a higher frequency of cognitive disorders (39%) compared to those without brain metastases (24.9%). **Mood disorders** including anxiety, depression, agitation and one case of suicide have also been reported. They generally occurred within 1 month of treatment (ranging from 1 day to 9 months).

Increases in liver function tests (AST and ALT) have been reported in clinical trials. The time to onset of elevated AST and ALT was 2 weeks (median) but ranged from 1 day to 29.5 months for AST and 1 day to 9.2 months for ALT.

Hyperuricemia has been reported, including 1 death due to tumor lysis syndrome. Hyperuricemia resolved in 73% of patients following initiation of urate-lowering medication without interruption or dose reduction of entrectinib.

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E - Dosing

Refer to protocol by which patient is being treated.

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

Solid tumours: NTRK fusion-positive status should be established using a validated test prior to initiation of entrectinib.

NSCLC: ROS1-positive status should be established using a validated test prior to initiation of entrectinib.

In patients with symptoms or known risk factors of CHF, LVEF should be assessed prior to initiation of entrectinib.

Adults:

Oral: 600 mg Daily

Dosage with Toxicity:

Dose Level	Entrectinib Dose (mg/day)
0	600
-1	400
-2	200
-3	Discontinue

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

Toxicity	Grade	Action
Anemia or Neutropenia	≥ Grade 3	Hold*; resume at same dose level or 1 dose level ↓.
CNS Effects	≥ Grade 2	Hold*; resume at 1 dose level ↓. If recurs, hold*; further ↓ 1 dose level. Discontinue if prolonged, severe, or intolerable events occur.
Hepatotoxicity	Grade 3	Hold*. If recovery in: • ≤ 4 weeks; resume at same dose level • > 4 weeks; discontinue

		If recurs, and recovery in: • ≤ 4 weeks; resume at 1 dose level ↓ • > 4 weeks; discontinue
	Grade 4	Hold*. If recovery in: • ≤ 4 weeks; resume at 1 dose level ↓ • > 4 weeks; discontinue If recurs; discontinue.
	ALT or AST > 3 x ULN with total bilirubin > 1.5 x ULN (in the absence of cholestasis or hemolysis)	Discontinue.
Hyperuricemia	Symptomatic or Grade 4	Hold until improvement of signs and/or symptoms . Initiate urate-lowering medication. Resume at same dose level or 1 dose level ↓.
Syncope	Any	Hold until recovered; resume at 1 dose level ↓. If recurs, hold until recovered; further ↓ 1 dose level or discontinue.
Congestive Heart Failure	Grade 2 or 3	Hold until recovery to ≤ grade 1; resume at 1 dose level ↓.
	Grade 4	Discontinue.
QT Interval Prolongation	QTc 481 to 500 msec	Hold until recovery to baseline; resume at same dose level.
	QTc >500 msec	Hold until recovery to baseline; If QT prolongation risk factors are: • Identified and corrected; resume at same dose level • **NOT** identified; resume at 1 dose level ↓
	Torsade de pointes; polymorphic ventricular	Discontinue.

	tachycardia; signs/symptoms of serious arrhythmia	
Vision Disorders	≥ Grade 2	Hold until improvement or stabilization; resume at same dose level or 1 dose level ↓.
All other toxicities	≥ Grade 3	Hold*. If recovery in: • ≤ 4 weeks; resume at same dose level or 1 dose level ↓ • > 4 weeks; discontinue
	Recurrent Grade 4	Discontinue.

*Resume when hematologic toxicities recovered to ≤ grade 2 or baseline and other specified toxicities recovered to ≤ grade 1 or baseline.

Dosage with Hepatic Impairment:

Hepatic impairment may increase the plasma concentration of entrectinib and/or its major active metabolite as entrectinib is primarily eliminated through metabolism in the liver.

Hepatic Impairment	Entrectinib Dose
Child-Pugh A	No dose adjustment required
Child-Pugh B	
Child-Pugh C	No dose adjustment required; closely monitor hepatic function and toxicities

Dosage with Renal Impairment:

The pharmacokinetics of entrectinib are not significantly affected by renal impairment.

Creatinine Clearance (mL/min)	Entrectinib Dose
≥ 30	No dose adjustment required
< 30	Has not been studied

Dosage in the elderly:

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

Dosage based on ethnicity:

No dose adjustment required.

Children:

Safety and efficacy in children have not been established. Entrectinib was associated with a higher risk of skeletal fractures in the pediatric population compared to adults.

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F - Administration Guidelines

- Administer with or without food.
- Capsules should be swallowed whole and not opened, crushed, chewed, or dissolved.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, a make-up dose can be administered unless the next dose is within 12 hours.
- If vomiting occurs immediately after the dose, the dose may be repeated.
- Store at room temperature (15-30°C).

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any components of the formulation.

Other Warnings/Precautions:

- Entrectinib contains lactose; consider use in patients with lactose intolerance, hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Patients with symptomatic CHF, myocardial infarction, unstable angina, or coronary artery bypass graft within three to six months of study entry were excluded from clinical trials.
- Entrectinib should be avoided in patients with congenital long QT syndrome.
- Caution with driving or using machinery as visual disturbances, dizziness, and syncope may occur with treatment.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Clastogenicity: No
- Mutagenicity: No
- Genotoxicity: Probable
- Teratogenicity: Probable
- Fetotoxicity: Yes
  Entrectinib is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **5 weeks** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **3 months** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **2 weeks** after the final dose.
- Fertility effects:
  Documented in male animals

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H - Interactions

CYP3A4 is the predominant enzyme mediating the metabolism of entrectinib and formation of its major active metabolite M5.

Entrectinib is a weak inhibitor of BCRP, OATP 1B1 and MATE1 and a weak P-gp substrate. Entrectinib is not a BCRP substrate, but M5 is a P-gp and BCRP substrate.

Entrectinib and M5 do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

No dose adjustment is required when entrectinib is co-administered with proton pump inhibitors or other drugs that raise gastric pH.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ entrectinib concentration and/or toxicity. (exposure of entrectinib was increased by 500% when given with itraconazole)	↓ metabolism of entrectinib	Avoid co-administration or limit concomitant use with strong or moderate CYP3A4 inhibitors to ≤14 days. If concomitant use of strong inhibitors cannot be avoided, reduce entrectinib dose to 100mg daily. If concomitant use of moderate inhibitors cannot be avoided, reduce entrectinib dose to 200mg daily. After discontinuation of strong or moderate CYP3A4 inhibitor for 3 to 5 t1/2, resume entrectinib dose from prior to initiating the inhibitor.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ entrectinib concentration and/or efficacy (exposure of entrectinib was reduced by 77% when given with rifampin)	↑ metabolism of entrectinib	Avoid concomitant use with CYP3A4 inducers.

Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	Enhance the QTc-prolonging effect	Additive	Avoid concomitant use with drugs that may prolong QT interval.
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ substrate concentration and/or toxicity. (exposure of midazolam increased by ~50%).	↓ metabolism of substrate	Caution and monitor with drugs with narrow therapeutic index.
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ substrate concentration and/or toxicity. (digoxin Cmax increased by 28% and AUC by 18%%, with minimal effect on digoxin clearance)	Entrectinib is a weak P-gp inhibitor	No dose adjustment required. Caution and monitor with drugs with narrow therapeutic index.

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I - Recommended Clinical Monitoring

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

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

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, at each visit and as clinically indicated
ECG	Baseline and as clinically indicated; more frequently in patients with risk factors such as CHF, electrolyte abnormalities, or concomitant medications known to prolong QT interval
LVEF	Baseline in patients with symptoms or known risk factors for CHF, and as clinically indicated
Liver function tests	Every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated
Electrolytes, uric acid levels	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Clinical toxicity assessment for signs/symptoms of edema, fatigue, fractures, cardiotoxicity, tumor lysis syndrome, visual changes, GI and CNS effects	As clinically indicated

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

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- entrectinib - For the treatment of locally advanced (not amenable to curative therapy) or metastatic NSCLC, according to clinical criteria
- entrectinib - Treatment of patients with unresectable locally advanced, or metastatic solid extracranial tumours documented to have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, according to specific criteria

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K - References

Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):271-282. doi:10.1016/S1470-2045(19)30691-6.

Dziadziuszko R, Krebs MG, De Braud F, et al. Updated integrated analysis of the efficacy and safety of entrectinib in locally advanced or metastatic ROS1 fusion-positive non-small-cell lung cancer. J Clin Oncol. 2021 Apr 10;39(11):1253-1263. doi: 10.1200/JCO.20.03025.

Prescribing Information: Rozlytrek® (entrectinib). Genentech USA, Inc. South San Francisco, CA. November 2021.

Product Monograph: Rozlytrek® (entrectinib). Hoffmann-La Roche Limited. November 9, 2023.

March 2024 Modified Dosage with toxicity and Dosage with hepatic toxicity sections

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L - Disclaimer

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

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