DRUG NAME: Entrectinib

SYNONYM(S): RXDX-101[1], NMS-E628[2]

COMMON TRADE NAME(S): ROZLYTREK®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Entrectinib is an orally administered, small molecule, multi-target tyrosine kinase inhibitor which targets tropomyosin-related kinase (Trk) proteins TrkA, TrkB, and TrkC, proto-oncogene tyrosine-protein kinase ROS (ROS1) and anaplastic lymphoma kinase (ALK). TrkA, TrkB, and TrkC are receptor tyrosine kinases encoded by the neurotrophic tyrosine receptor kinase (NTRK) genes NTRK1, NTRK2, and NTRK3, respectively. Fusion proteins that include Trk, ROS1, or ALK kinase domains drive tumorigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. By potently inhibiting the Trk kinases, ROS1, and ALK, entrectinib inhibits downstream signalling pathways, cell proliferation and induces tumour cell apoptosis.[3-5]

PHARMACOKINETICS:

Oral Absorption	bioavailability = 55%; T_{max} = 4-6 hours; T_{max} delayed 2 h by high-fat, high-calorie food intake	
Distribution	highly bound to human plasma proteins	
	cross blood brain barrier?	yes
	volume of distribution	551 L (entrectinib); 81.1 L (M5)
	plasma protein binding	>99% (entrectinib and M5)
Metabolism	primarily metabolized by CYP 3A4	
	active metabolite(s)	M5
	inactive metabolite(s)	M11
Excretion	primarily via hepatic clearance	
	urine	3.06%
	feces	82.9% (36% as unchanged entrectinib, 22% as M5)
	terminal half life	20 h (entrectinib); 40 h (M5)
	clearance	19.6 L/h (entrectinib); 52.4 L/h (M5)
Elderly	no clinically significant difference	
Children	comparable pharmacokinetics of entrectinib and M5 in adults and children	
Ethnicity	no clinically significant difference	

Adapted from standard reference[3,4] unless specified otherwise.

USES:

Primary uses:

*Lung cancer, non-small cell

*Solid tumours, NTRK gene fusion-positive

*Health Canada approved indication

Other uses:

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SPECIAL PRECAUTIONS:

Caution:
- ***congestive heart failure*** (CHF) has been reported; patients with symptomatic CHF or known risk factors of CHF require LVEF assessment prior to treatment[3]
- ***starting dose reduction*** may be required for some CYP 3A4 interactions[3]
- ***QT prolongation*** has been reported; avoid use in patients with congenital long QT syndrome or taking medications known to prolong the QT interval, and monitor ECG and electrolytes during treatment[3,4]

Special populations: Safety and efficacy in ***pediatric*** patients has not been established. Entrectinib is associated with a higher incidence of skeletal fractures (with minimal or no trauma) in the pediatric population (23%) compared to adults (5-6%). In juvenile animal studies, decreased weight gain, delayed sexual maturation, neurobehavioural deficits (e.g., in learning and memory), and decreased femur length were observed at exposures lower than those seen following human clinical exposure.[3,4]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test; not clastogenic or aneugenic in mammalian *in vivo* chromosome tests. Entrectinib is possibly aneugenic in mammalian *in vitro* chromosome tests.[3]

Fertility: In animal studies, dose-dependent decreases in prostate weight were observed at exposures higher than those seen following human clinical exposure, but there were no other observed effects on male and female reproductive organs.[3]

Pregnancy: In animal studies, lower fetal weights and reduced skeletal ossification were observed at exposures lower and approximately equal to those seen following human clinical exposure. At exposures higher than those seen following human clinical exposure, maternal toxicity (decreased weight gain and food consumption) and fetal malformations (body closure defects, malformations of the vertebrae, limbs and ribs) were observed. Women of childbearing potential should use effective contraception during treatment and for 5 weeks following the last dose. Men with female partners of childbearing potential should use effective contraception during treatment and for 3 months following the last dose.[3,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 14 days following the last dose.[3]

SIDE EFFECTS:

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

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (28-67%, severe 9-11%)
	lymphopenia (40%, severe 12%)
	neutropenia (12-28%, severe 5-7%)
cardiac	***congestive heart failure*** (3%, severe 2%); median time to onset 2 months

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Revised:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	myocarditis (severe <1%)
eye	***visual disorders*** (21%, severe <1%); see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low[7]
	abdominal pain (13-16%, severe <1%)
	constipation (46%, severe <1%)
	diarrhea (35%, severe 2%)
	dysphagia (10%, severe <1%)
	large intestine perforation (severe <1%); fatal events reported
	nausea (34%, severe <1%)
	vomiting (24%, severe <1%)
general disorders and administration site conditions	***edema*** (40%, severe 1%)
	fatigue (48%, severe 5%)
	pain (28%, severe 2%)
	pyrexia (21%, severe <2%)
infections and infestations	lung infection (10-13%, severe 5-6%)
	pneumonia (severe 4%); fatal events reported
	sepsis (severe 3%); fatal events reported
	urinary tract infection (13%, severe 2-3%)
injury, poisoning, and procedural complications	***bone fractures*** (5-6%); median time to fracture 4 months; mostly hip, femoral or tibial shaft fractures
	falls (8%)
investigations	alkaline phosphatase increase (25%, severe <1%)
	ALT increase (14-38%, severe 3%); median time to onset 2 weeks
	amylase increase (26%, severe 5%)
	AST increase (16-44%, severe 3%); median time to onset 2 weeks
	blood creatinine increase (23-73%, severe 2%)
	lipase increase (28%, severe 10%)
	QT interval prolongation (2-3%)
metabolism and nutrition	appetite decrease (13%, severe <1%)
	dehydration (10%, severe 1%)
	hyperglycemia (severe 4%)
	hyperkalemia (25%, severe 2%)
	hypernatremia (35%, severe <1%)
	hyperuricemia (9-52%, severe 2-10%)
	hypoalbuminemia (28%, severe 3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypocalcemia (34%, severe 2%)
	hypophosphatemia (30%, severe 7%)
	tumour lysis syndrome (severe <1%); fatal events reported
	weight increase (25%, severe 7%)
musculoskeletal and connective tissue	arthralgia (21%, severe <1%)
	back pain (12%, severe 1%)
	muscular weakness (12%, severe <1%)
	myalgia (21-28%, severe 1%)
	pain in extremity (11%, severe <1%)
nervous system see paragraph following **Side Effects** table	ataxia (17%, severe <1%)
	cognitive disorders (26-27%, severe 5%)
	dizziness (38%, severe <2%)
	dysesthesia/paresthesia (29-34%, severe <1%)
	dysgeusia (44%, severe <1%)
	headache (18%, severe <1%)
	mood disorders (10%, severe <1%); median time to onset 1 month
	peripheral sensory neuropathy (18%, severe 1%)
	sleep disorders (14%, severe <1%)
	syncope (4%, severe 3%)
renal and urinary	urinary retention (5%)
respiratory, thoracic and mediastinal	cough (24%, severe <1%)
	dyspnea (30%, severe 4-6%)
	hypoxia (4%, severe 3%)
	pleural effusion (8%, severe 3%)
	respiratory failure (severe 2%)
skin and subcutaneous tissue	rash (11%, severe <1%)
vascular	hypotension (18%, severe 3%)
	pulmonary embolism (severe 3-4%)

Adapted from standard reference[1,3,4] unless specified otherwise.

A broad spectrum of ***central nervous system*** (CNS) adverse reactions are reported. Patients with brain metastases previously treated with CNS irradiation may be at increased risk of dizziness, headache, balance disorder, paresthesia, and confusional states. Cognitive disorders are reported in up to 27% of patients and can include confusion, mental status changes, disturbance in attention, memory impairment, amnesia, delirium, aphasia, and hallucinations. In the majority of patients, cognitive symptoms occur within 3 months of starting treatment. Dose interruption, dose reduction, or treatment discontinuation may be required.[1,3,4] Withdrawal pain has been associated

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Revised:

with Trk inhibitors as a class effect and is more common in patients who have been on treatment for 6 months or longer. Withdrawal pain is defined as pain experienced with temporary or permanent Trk inhibitor discontinuation and may present as full-body ache, muscle pain, allodynia, and/or headache. Median time to onset after treatment discontinuation is 2 days. Trk inhibitor reinitiation has been an effective management intervention.[8]

Visual disorders are reported in 21% of patients and can include blurred vision, photophobia, diplopia, visual impairment, photopsia, cataract, and vitreous floaters. Consider ophthalmological evaluation in patients with new visual changes or changes that interfere with activities of daily living. Dose interruption or dose reduction may be required.[3,4]

INTERACTIONS :

AGENT	EFFECT	MECHANISM	MANAGEMENT
digoxin[3,4]	18% increase in AUC and 28% increase in C_{max} of digoxin	weak P-gp inhibition by entrectinib	not considered clinically significant; no dose adjustment required
grapefruit juice[3,4]	may increase plasma level of entrectinib	may inhibit CYP 3A4 metabolism of entrectinib in the intestinal wall	avoid grapefruit juice for 48 hours before and for duration of entrectinib therapy
itraconazole[3,4]	604% increase in AUC and 173% increase in C_{max} of entrectinib	strong CYP 3A4 inhibition by itraconazole	avoid concurrent use or limit to 14 days; if unavoidable, reduce entrectinib dose to 100 mg PO once daily and monitor for entrectinib toxicity
lansoprazole[3,4]	25% decrease in AUC and 23% decrease in C_{max} of entrectinib	pH-dependent solubility of entrectinib (i.e., reduced entrectinib solubility with increasing pH)	not considered clinically significant; no dose adjustment required
midazolam[3,4]	50% increase in AUC and 21% decrease in C_{max} of midazolam	weak CYP 3A4 inhibition by entrectinib	no dose adjustment required
rifampin[3,4]	77% decrease in AUC and 56% decrease in C_{max} of entrectinib	strong CYP 3A4 induction by rifampin	avoid concurrent use

Entrectinib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentration of entrectinib. Avoid concurrent use with *moderate* or *strong* CYP 3A4 *inhibitors* or limit to 14 days or less if possible. If coadministration cannot be avoided, entrectinib dose reduction is required. For coadministration with a *moderate* inhibitor, reduce entrectinib dose to 200 mg PO once daily. For coadministration with a *strong* inhibitor, reduce entrectinib dose to 100 mg PO once daily. After discontinuation of the concurrent inhibitor, entrectinib may be resumed at the prior dose; a wash-out period may be required for inhibitors with a long half-life. CYP 3A4 ***inducers*** may decrease the plasma concentrations of entrectinib; avoid concurrent use.[3,4]

In vitro, entrectinib is a weak inhibitor of BCRP (not considered clinically significant). *In vitro*, M5 is a substrate of BCRP; clinical significance is unknown.[3]

In vitro, entrectinib is a weak inhibitor of CYP 3A4, organic anion-transporting polypeptide (OATP) 1B1 and multidrug and toxin extrusion protein 1 (MATE1). Entrectinib and M5 are substrates of P-gp. Clinical significance is unknown.[3,4]

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Revised:

SUPPLY AND STORAGE:

Oral: Hoffman-La Roche Limited supplies entrectinib as 100 mg and 200 mg hard-shell capsules. Capsules contain lactose. Store at room temperature.[3]

DOSAGE GUIDELINES:

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

Adults:

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

Oral:[3]

600 mg (range 100-600 mg) PO once daily

Administer with food or on an empty stomach.
Do not take with grapefruit or grapefruit juice.

Concurrent radiation:

no information found

Dosage in myelosuppression:

modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure:

creatinine clearance ≥ 30 mL/min: no adjustment required[3,4]
creatinine clearance < 30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

mild hepatic impairment (total bilirubin ≤ 1.5 x ULN): no adjustment required[3,4]
moderate/severe hepatic impairment: no information found

Dosage in dialysis:

no information found

Children:

Oral:[4]

recommended dosage in pediatric patients 12 years of age and older:

Body Surface Area (BSA)	Recommended Dosage
0.91 to 1.10 m^2	400 mg PO once daily
1.11 to 1.50 m^2	500 mg PO once daily
> 1.5 m^2	600 mg PO once daily

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