

Regimen Monograph

[Regimen Name](#) | [Drug Regimen](#) | [Cycle Frequency](#) | [Premedication and Supportive Measures](#) | [Dose Modifications](#) | [Adverse Effects](#) | [Interactions](#) | [Drug Administration and Special Precautions](#) | [Recommended Clinical Monitoring](#) | [Administrative Information](#) | [References](#) | [Other Notes](#) | [Disclaimer](#)

A - Regimen Name

ENTR Regimen

entrectinib

Disease Site Solid Tumours (Extracranial)

Intent Palliative

Regimen Category Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of unresectable locally advanced, or metastatic solid extracranial tumours* with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and without a known acquired resistance mutation, in patients:

- with good performance status, AND
- who have progressed on all standard treatment for their tumour site, AND
- where surgery is not an option

*includes patients who have brain metastases that are controlled or asymptomatic but NOT in patients who have primary CNS tumours

Supplementary [entrectinib](#)**Public Funding**

Exceptional Access Program (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) ([EAP Website](#))

[back to top](#)

B - Drug Regimen[entrectinib](#)

600 mg

PO

Daily

[back to top](#)

C - Cycle Frequency**CONTINUOUS TREATMENT**

Until disease progression or unacceptable toxicity

[back to top](#)

D - Premedication and Supportive Measures

Antiemetic Regimen: Low – No routine prophylaxis; PRN recommended

- Also refer to [CCO Antiemetic Recommendations](#).

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

[back to top](#)

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

NTRK fusion-positive status should be established using a validated test prior to initiating therapy.

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

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: <ul style="list-style-type: none"> • ≤ 4 weeks; resume at same dose level • > 4 weeks; discontinue If recurs, and recovery in: <ul style="list-style-type: none"> • ≤ 4 weeks; resume at 1 dose level ↓ • > 4 weeks; discontinue

	Grade 4	Hold*. If recovery in: <ul style="list-style-type: none"> • ≤ 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: <ul style="list-style-type: none"> • Identified and corrected; resume at same dose level • NOT identified; resume at 1 dose level ↓
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	Discontinue.
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: <ul style="list-style-type: none"> • ≤ 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.

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

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.

[back to top](#)

F - Adverse Effects

Refer to [entrectinib](#) drug monograph(s) for additional details of adverse effects.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
<ul style="list-style-type: none"> • Fatigue • Constipation • Dysgeusia • Edema • Dizziness • Diarrhea • Nausea, vomiting • Cough, dyspnea • Dysesthesia (including peripheral neuropathy) • Myelosuppression ± infection • Cognitive disturbance • Weight gain 	<ul style="list-style-type: none"> • Creatinine increased • Eye disorders • Musculoskeletal pain • Headache • Hypotension • Ataxia • ↑ LFTs • Sleep disorder • Anorexia • Rash • Mood changes 	<ul style="list-style-type: none"> • Cardiotoxicity • QT interval prolonged • Syncope • Hyperuricemia • Fracture

[back to top](#)

G - Interactions

Refer to [entrectinib](#) drug monograph(s) for additional details.

- Avoid co-administration or limit concomitant use with strong or moderate CYP3A4 inhibitors to ≤14 days as combination may increase entrectinib concentration and/or toxicity.
 - 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 half-lives, resume entrectinib dose from prior to initiating the inhibitor.

-
- Avoid concomitant use with CYP3A4 inducers as combination may decrease entrectinib concentration and/or efficacy.
 - Avoid concomitant use of with drugs that may prolong QT interval as combination may enhance QT-prolonging effects.

[back to top](#)

H - Drug Administration and Special Precautions

Refer to [entrectinib](#) drug monograph(s) for additional details.

Administration

- 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).

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.

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.

Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

- Fertility Effects: Probable

[back to top](#)

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

- 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

[back to top](#)

J - Administrative Information

Outpatient prescription for home administration

[back to top](#)

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 Feb;21(2):271-82.

Entrectinib Drug Monograph, Ontario Health (Cancer Care Ontario).

CADTH reimbursement recommendation: Entrectinib (For the treatment of adults with unresectable locally advanced or metastatic extracranial solid tumours), November 2022.

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

[back to top](#)

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the [New Drug Funding Program](#) or [Ontario Public Drug Programs](#) websites for the most up-to-date public

funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

[back to top](#)