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

LORL Regimen

Lorlatinib

Disease Site
Lung
Non-Small Cell

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
First-line treatment of ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC, in patients with good performance status

Supplementary Public Funding
lorlatinib
Exceptional Access Program (lorlatinib - For the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer.) (EAP Website)

back to top

B - Drug Regimen

lorlatinib	100 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: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

- Blood pressure should be controlled prior to initiation of lorlatinib.

Also refer to CCO Antiemetic Recommendations.

back to top

E - Dose Modifications

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

Patients must have a documented ALK-positive status, based on a validated ALK assay, prior to starting treatment with lorlatinib.

Dosage with toxicity

Dose level	Dose (mg/day)
0	100
-1	75
-2	50
-3	Discontinue

Dose Modification for Toxicity:

Toxicity	Grade	Action
Hypercholesterolemia	Grade 1 or 2 (ULN to 10.34 mmol/L)	Continue at same dose level. Introduce or modify lipid-lowering therapy.
	Grade 3 (10.35 to 12.92 mmol/L)	Continue at same dose level. Introduce lipid-lowering therapy. If currently on lipid-lowering therapy, increase the dose of this therapy or change to a new lipid-lowering therapy.
	Grade 4 (>12.92 mmol/L)	Hold.* Introduce lipid-lowering therapy. If currently on lipid-lowering therapy, increase the dose of this therapy or change to a new lipid-lowering therapy Resume at same dose level. If recurs despite maximal lipid-lowering therapy, resume at 1 dose level ↓.
Hypertriglyceridemia	Grade 1 or 2 (1.71 to 5.7 mmol/L)	Continue at same dose level Introduce or modify lipid-lowering therapy.
	Grade 3 (5.71 to 11.4 mmol/L)	Continue at same dose level. Introduce lipid-lowering therapy. If currently on lipid-lowering therapy, increase the dose of this therapy or change to a new lipid-lowering therapy.
	Grade 4 (>11.4 mmol/L)	Hold.* Introduce lipid-lowering therapy. If currently on lipid-lowering therapy, increase the dose of this therapy or change to a new lipid-lowering therapy Resume at same dose level. If recurs despite maximal lipid-lowering therapy, resume at 1 dose level ↓.

Central Nervous System Effects (e.g., psychotic effects [including hallucination], changes in cognitive function, mood, speech, or mental status)	Grade 1	Continue at same dose level. OR Hold dose until recovery to baseline. Resume at same dose or 1 dose level ↓.
	Grade 2 or 3	Hold dose*. Resume at 1 dose level ↓.
	Grade 4	Discontinue.
Symptoms of Interstitial Lung Disease (ILD)/Pneumonitis (treatment–related)		Discontinue.
Hypertension	Grade 3	Hold.* Resume at same dose level. If recurs, hold* and resume with at least 1 dose level ↓. If adequate control cannot be achieved, discontinue.
	Grade 4	Hold.* Resume with at least 1 dose level ↓.or discontinue. If recurs, discontinue.
Hyperglycemia	Grade 3 (> 13.9 mmol/L despite anti-hyperglycemic therapy)	Hold until adequately controlled. Resume at 1 dose level ↓. If adequate control cannot be achieved, discontinue.
	Grade 4	
All other toxicity	Grade 1 or 2	Continue at same dose or at 1 dose level ↓ as clinically indicated.
	≥ Grade 3	Hold.* Resume at 1 dose level ↓.

*Do not restart treatment until hypercholesterolemia/hypertriglyceridemia resolve to ≤ Grade 2, other non-CNS toxicities resolve to ≤ Grade 2 or baseline and CNS toxicities or hypertension resolve to ≤ Grade 1.

Dose modifications for PR Prolongation/AV Block:

	Asymptomatic	Symptomatic
	Action	
First-degree AV block	Continue at same dose level. Monitor closely.[1,2]	Hold. Monitor closely.[1,2] If symptoms resolve, resume at same dose level or at 1 dose level ↓.
Second-degree AV block	Hold. Monitor closely.[1,2] If subsequent ECG does not show second-degree block, resume at same dose level or 1 dose level ↓.	Hold. Monitor closely.[1] Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic AV block persists. If symptoms and the second-degree block resolve or if patients revert to asymptomatic first-degree AV block, resume at 1 dose level ↓.
Complete AV Block	Hold.[1] Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated. If AV block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, resume at full dose. If no pacemaker placed, resume at 1 dose level ↓ only when symptoms resolve AND PR interval is less than 200 msec.	

[1]Assess medications and electrolyte imbalance that may prolong PR interval.
[2]Monitor ECG/symptoms potentially related to AV block closely.

Hepatic Impairment

Hepatic impairment	Lorlatinib Dose
Mild (total bilirubin ≤ ULN with AST > ULN or total bilirubin >1 to 1.5 x ULN with any AST)	No dose adjustment required.
Moderate or Severe	No data available.

Renal Impairment

Renal impairment	Lorlatinib Starting Dose
Mild or Moderate (CrCl ≥ 30 mL/min)	No dose adjustment required.
Severe (CrCl < 30 mL/min)	75 mg daily
Requiring dialysis	Not recommended. Limited data available.

Dosage in the Elderly

No dose adjustment required. The following adverse events were more frequently reported in elderly patients in clinical trials: cognitive effects, dyspnea, fatigue, arthralgia, diarrhea, anemia, myalgia, vomiting, back pain and rash. No clinically relevant differences in safety and efficacy were observed between patients ≥ 65 years and younger patients.

back to top

F - Adverse Effects

Refer to lorlatinib drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• ↑ Cholesterol (may be severe) • ↑ Triglycerides (may be severe) • Edema	• Weight gain • Peripheral neuropathy	• CNS effects* (may be severe) • Diarrhea • Cough, dyspnea (may be severe) • Fatigue • Musculoskeletal pain • Anemia • Hypertension (may be severe) • Visual disorders • ↑ LFTs • Headache • Constipation • Nausea, vomiting • Rash	• Arterial/venous thromboembolism • AV block • QT interval prolongation • Pneumonitis • Respiratory failure • Hyperglycemia • ↑ Amylase / lipase • Myelosuppression (neutropenia)

*These included changes in cognitive function, mood, speech, mental status, and sleep; seizures and psychotic effects were uncommon.

back to top

G - Interactions

Refer to lorlatinib drug monograph(s) for additional details.

- CONTRAINDICATED with strong CYP3A4 inducers due to increased risk of severe hepatotoxicity and/or decreased lorlatinib concentration. Discontinue strong CYP3A4 inducers for at least 3 plasma half-lives before starting lorlatinib.
- Avoid co-administration with strong CYP3A4 inhibitors due to increased risk of toxicity. If co-administration is unavoidable, ↓ lorlatinib dose to 75 mg daily. If the strong CYP3A4 inhibitor is

discontinued, resume at the dose used prior to initiation of the strong CYP3A4 inhibitor, after a washout period of 3 to 5 half-lives of the CYP3A4 inhibitor.
- Avoid use with fluconazole due to increased risk of toxicity. If co-administration is unavoidable, ↓ lorlatinib dose to 75 mg daily.
- Avoid moderate CYP3A4 inducers due to increased risk of hepatotoxicity (theoretical) and/or decreased lorlatinib concentration. If co-administration is unavoidable, ↑ lorlatinib dose to 125 mg daily.
- Avoid co-administration with CYP3A4 substrates with narrow therapeutic index due to possible ↓ substrate concentration and/or efficacy.

back to top

H - Drug Administration and Special Precautions

Refer to lorlatinib drug monograph(s) for additional details.

Administration

- Lorlatinib should be taken at approximately the same time each day with or without food.
- Tablets should be swallowed whole and should not be chewed, crushed or split.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during lorlatinib treatment.
- If a dose is missed, patient may take if there are ≥ 4 hours until the next dose. If there are < 4 hours until the next dose, the dose should be skipped and the next dose should be taken at the scheduled time. Patients should not take 2 doses at the same time to make up for a missed dose.
- If the patient vomits after taking lorlatinib, do not give an extra dose; give the following dose at the next scheduled time.
- Store at room temperature (15ºC to 30ºC) in the original package. Protect from light.

Contraindications

- Patients who are hypersensitive to this drug or any components of the formulation
- Concomitant use of strong CYP3A inducers due to the potential for serious hepatotoxicity (Refer to Interactions section)

Warnings/Precautions

- Avoid concomitant use of lorlatinib with moderate CYP3A inducers.
- Lorlatinib should not be used in patients with severe acute or chronic medical or psychiatric conditions, including recent or active suicidal ideation or behaviour. (Refer to EAP criteria.) Some exclusion criteria from the clinical trial included the presence of chronic or uncontrolled conditions, such as vascular or nonvascular conditions, predisposing characteristics for acute

pancreatitis, lung disease, or psychiatric conditions. (See full details in Shaw et al.)
- Patients at risk for AV block/PR prolongation should be monitored closely.
- Use caution when driving or operating machinery due to CNS effects.
- Tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

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
    - Patients wishing to have children in the future should seek advice on effective fertility preservation before treatment.

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.

Recommended Clinical Monitoring

- Liver function tests; Baseline and as clinically indicated. (If co-administration with a moderate CYP3A inducer is unavoidable: 48 hours after initiating lorlatinib and at least 3 times during the first week after initiation.)

- ECG; Baseline, monthly (especially in patients with risk factors for clinically significant cardiac events), and as clinically indicated

- Blood pressure; Baseline, 2 weeks after initiation, and at least monthly during treatment

- Cholesterol and triglycerides; Baseline, 2, 4, and 8 weeks after initiation, and as clinically indicated

- Lipase, amylase; Baseline and as clinically indicated
- Blood glucose; Baseline and as clinically indicated
- Clinical toxicity assessment for CNS adverse events (e.g. hallucination, seizure, and changes in cognition, mood, mental status, or speech), edema, peripheral neuropathy, thromboembolism, GI effects and pneumonitis; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

K - References

CADTH Reimbursement Recommendation: Lorlatinib (monotherapy for first-line ALK-positive locally advanced or metastatic NSCLC). April 2022.

Lorlatinib drug monograph. Ontario Health (Cancer Care Ontario).

Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. N Engl J Med. 2020 Nov 19;383(21):2018-2029. doi: 10.1056/NEJMoa2027187.

Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018;19:1654-67.

PEBC Advice Documents or Guidelines

- Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO and OH(CCO) Joint Guideline Update

August 2023 Modified Rationale and uses, Dose modifications, Warnings/Precautions, and Pregnancy/lactation sections; added EAP funding information

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

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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.

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back to top