Drug Monograph

A - Drug Name

lorlatinib

COMMON TRADE NAME(S): Lorbrena®

back to top

B - Mechanism of Action and Pharmacokinetics

Lorlatinib is a selective, reversible, inhibitor of ALK and ROS1 tyrosine kinases. It has demonstrated activity against multiple mutant forms of the ALK enzyme that may be resistant to first and second generation ALK inhibitors.

Absorption	Rapidly absorbed	
	Bioavailability	81%
	Effects with food	Food has no clinically important effects. Administration with a high fat, high calorie meal resulted in a 5% increase in AUC and 9% decrease in Cmax compared to overnight fasting.
	T max	1.2 hours following a single 100 mg dose; 2 hours following 100 mg once daily multiple dosing.
Distribution	Cross blood brain barrier?	Yes
	PPB	66% with moderate binding to both albumin and α1-acid glycoprotein.

Metabolism	Oxidation and glucuronidation are the primary metabolic pathways by CYP3A4 and UGT1A4, with minor contribution from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.	
	Inactive metabolites	Yes
Elimination	Urine	48% (< 1% as unchanged drug)
	Feces	41% (9% as unchanged drug)
	Half-life	24 hours (plasma)

back to top

C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer (NSCLC)

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

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects include those reported in ≥ 10% of patients in a randomized, multicenter Phase III study of previously untreated ALK-positive metastatic NSCLC patients on lorlatinib compared to crizotinib. Severe or life-threatening adverse events from other studies or post-marketing may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial/venous thromboembolism (rare)	E
	Atrioventricular block (2%)	E
	Hypertension (18%) (10% severe)	E
	QT interval prolonged (1%) (> 500 msec)	E
Dermatological	Rash (11%)	E
Gastrointestinal	Constipation (17%)	E
	Diarrhea (22%)	E
	Nausea, vomiting (15%)	E
	Weight gain (38%)	D
General	Edema (56%)	E
	Fatigue (20%)	E D
Hematological	Anemia (19%)	E D
	Myelosuppression ± infection (7%) (neutropenia)	E D
Hepatobiliary	↑ Amylase / lipase (9%)	E
	↑ LFTs (17%)	E
Metabolic / Endocrine	↑ Cholesterol (70%) (16% severe)	E
	Hyperglycemia (9%) (3% severe)	E
	↑ Triglycerides (64%) (20% severe)	E
Musculoskeletal	Musculoskeletal pain (19%)	E
Nervous System	Cognitive disturbance (22%)	D
	Dizziness (11%)	E
	Hallucinations (3%)	E
	Headache (17%)	E
	Mood changes (16%)	D
	Other - speech effects (7%)	D
	Peripheral neuropathy (34%) (2% severe)	D

	Seizure (2%)	E
	Sleep disorder (11%)	E
Ophthalmic	Visual disorders (18%)	E
Respiratory	Cough, dyspnea (20%) (3% severe)	D
	Pneumonitis (2%) (severe or life-threatening)	E D
	Respiratory failure (3%)	E D

* "*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 lorlatinib include ↑ cholesterol, ↑ triglycerides, edema, weight gain, peripheral neuropathy, cognitive disturbance, diarrhea, cough, dyspnea, fatigue and anemia.

Lorlatinib has been associated with **hypercholesterolemia** and **hypertriglyceridemia**. The median onset for both was 15 days. The median duration was 451 and 427 days, respectively. A majority of patients with hypercholesterolemia and hypertriglyceridemia required initiation of lipid-lowering medications, usually at ~17 days after lorlatinib initiation.

Hyperglycemia has also occurred with lorlatinib with a median onset of ~5 months.

Central nervous system (CNS) effects have been reported with lorlatinib. The effects were generally mild, transient, and reversible upon dose delay and/or dose reduction. The median time to first onset of any CNS effect was 1.4 months (1 day to 3.4 years).

PR interval prolongation and **Atrioventricular (AV) block** events have been reported in patients receiving lorlatinib. During clinical trials, 1 patient (0.2%) experienced Grade 3 AV block and underwent pacemaker placement.

Hypertension including grade 4 events were reported. The median time to onset of hypertension was 6.4 months (1 day to 2.8 years).

back to top

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.

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

Blood pressure should be controlled prior to initiation of lorlatinib.

Adults:

Oral: 100 mg Daily

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.

Dosage with 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.

Dosage with 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.

Children:

Safety and efficacy in children have not been established.

back to top

F - Administration Guidelines

- 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.

back to top

G - Special Precautions

Contraindications:

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

Other 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.

Other Drug Properties:

- Carcinogenicity: Unknown
  Carcinogenicity studies have not been performed.

Pregnancy and Lactation:

- Genotoxicity: No
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Pregnancy:
  Lorlatinib 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 **21 days** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **97 days** after the last dose.
  - A highly effective non-hormonal contraception method is required for patients who can get pregnant during lorlatinib treatment. If a hormonal contraception method must be used, a condom must be used together with the hormonal contraception.
- Breastfeeding:
  Breastfeeding is not recommended during treatment, and for **7 days** after the last dose.
- Fertility effects: Probable
  Documented in animal studies. Discuss fertility preservation with patients prior to starting treatment.

back to top

H - Interactions

Lorlatinib is metabolized primarily by CYP3A4 and UGT1A4, with minor contributions from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.

Lorlatinib induces CYP3A4 and, *in vivo*, results in weak induction of CYP2C9, UGT and CYP2B6. Concurrent use of lorlatinib with CYP2B6 substrates may result in decreased plasma concentrations of the substrate.

Lorlatinib has the potential to inhibit BCRP, OCT1, MATE1, and OAT3.

Severe hepatotoxicity has occurred in 10 of 12 patients receiving a single dose of lorlatinib with multiple daily doses of a strong CYP3A inducer (i.e. rifampin). ALT or AST elevations occurred within 3 days and returned to normal after a median of 15 days (7 to 34 days); the median time to recovery was 18 days in patients with Grade 3 or 4 ALT or AST elevations and 7 days in patients with Grade 2 ALT or AST elevations.

No dose adjustment is necessary with proton pump inhibitors, H2 receptor antagonists, or antacids.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ lorlatinib concentration (↑ AUC by 42% and ↑ Cmax by 24% with itraconazole) and/or toxicity	↓ metabolism of lorlatinib	Avoid use with strong CYP3A4 inhibitors. Consider alternative with less CYP3A4 inhibition. If co-administration with a strong CYP3A4 inhibitor 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.
Fluconazole	↑ lorlatinib concentration and/or toxicity	↓ metabolism of lorlatinib	Avoid use with fluconazole. If co-administration is unavoidable, ↓ lorlatinib dose to 75 mg daily.
Strong CYP3A4 inducers (i.e. phenytoin, rifampin, carbamazepine, enzalutamide, St. John's Wort, etc)	↑ risk of severe hepatotoxicity and/or ↓ lorlatinib concentration (↓ AUC by 85% and ↓ Cmax by 76% with rifampin)	↑ metabolism of lorlatinib	CONTRAINDICATED with strong CYP3A4 inducers. Discontinue strong CYP3A4 inducers for at least 3 plasma half-lives before starting lorlatinib.
Moderate CYP3A4 inducers (i.e. bosentan, efavirenz, etravirine, phenobarbital, primidone)	↑ risk of hepatotoxicity (theoretical) and/or ↓ lorlatinib concentration	↑ metabolism of lorlatinib	Avoid use with moderate CYP3A4 inducers. If co-administration is unavoidable, ↑ lorlatinib dose to 125 mg daily.
CYP3A4 substrates (e.g. hormonal	↓ substrate concentration and/or efficacy	Lorlatinib is a CYP3A4 inducer.	Avoid with drugs with narrow therapeutic index.

contraceptives, cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)			
P-glycoprotein substrates with narrow therapeutic index (i.e. digoxin)	↓ substrate concentration and/or efficacy	Lorlatinib is a P-gp inducer in vivo.	Caution if drugs with narrow therapeutic index.

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

Monitor Type	Monitor Frequency
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

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- lorlatinib - For the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer.

back to top

K - References

Lorlatinib. Lexicomp, Inc. Accessed Jan 22, 2020.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Antiemesis: Version 2.2022, 2022.

Prescribing Information: Lorbrena (lorlatinib). Pfizer Inc. March 2021.

Product Monograph: Lorbrena (lorlatinib). Pfizer Canada ULC. May 16, 2022.

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.

February 2025 Updated Pregnancy/Lactation section

back to top

L - Disclaimer

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