Product Monograph

Including Patient Medication Information

PrLORBRENA®

Lorlatinib

Tablets

For oral use

25 and 100 mg of lorlatinib

Tyrosine Kinase Inhibitor

Antineoplastic agent

Pfizer Canada ULC

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Kirkland, Quebec
H9J2M5
Pfizer.ca

Date of Authorization:

2026-02-11

Control Number: 302451

Recent Major Label Changes

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Sections or subsections that are not applicable at the time of authorization are not listed.

Part 1: Healthcare Professional Information

1. Indications

LORBRENA (lorlatinib) is indicated as:

- monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC)
- monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib.

  The marketing authorization for the second and later line indication was based on a primary efficacy endpoint of tumor objective response rate and duration of response; no overall survival benefit has been demonstrated (see 14. Clinical Trials).

1.1. Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): Of the patients in Study B7461001 (N=295) and Study B7461006 (N=149) who received 100 mg LORBRENA orally once daily, 54 (18%) and 59 (40%), respectively, were aged 65 years or older. No clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients (see 10. Clinical Pharmacology).

2. Contraindications

- LORBRENA (lorlatinib) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6. Dosage Forms, Strengths, Composition, and Packaging.
- Concomitant use of strong CYP3A inducers with LORBRENA is contraindicated due to the potential for serious hepatotoxicity (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] elevations (see 4. Dosage and Administration and 9. Drug Interactions).

3. Serious Warnings and Precautions Box

- Hypercholesterolemia/Hypertriglyceridemia (see 7. Warnings and Precautions, Endocrine and Metabolism, *Hyperlipidemia*)
- Pneumonitis (see 7. Warnings and Precautions, Respiratory, *ILD/Pneumonitis*)
- Hepatotoxicity (see 7. Warnings and Precautions, General, Drug-Drug Interactions
- , *Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers*)

LORBRENA should only be prescribed and supervised by a qualified physician experienced in the use of antineoplastic agents.

4. Dosage and Administration

4.1. Dosing Considerations

- **Strong cytochrome P-450 (CYP)3A inhibitors:** Concurrent use of LORBRENA (lorlatinib) with strong CYP3A inhibitors may increase lorlatinib plasma concentrations. Concomitant use of LORBRENA with strong CYP3A inhibitors should be avoided. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered (see 9. Drug Interactions). If a strong CYP3A inhibitor must be co administered concomitantly, the LORBRENA dose of 100 mg once daily should be reduced to once daily 75 mg dose (see 9. Drug Interactions and 10. Clinical Pharmacology). If concurrent use of a strong CYP3A inhibitor is discontinued, LORBRENA should be resumed at the dose used prior to the initiation of the strong CYP3A inhibitor and after a washout period of 3 to 5 half lives of the CYP3A inhibitor.
- **Dosing modification for Fluconazole:** Avoid concomitant use of LORBRENA with fluconazole, based on Physiologically-Based Pharmacokinetic (PBPK) simulation. If concomitant use is unavoidable, reduce the starting dose of LORBRENA to 75 mg once daily.
- **Strong CYP3A inducers:** LORBRENA is contraindicated in patients taking strong CYP3A inducers. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating LORBRENA.
- **Moderate CYP3A inducers:** Avoid concomitant use with moderate CYP3A inducers as they may reduce lorlatinib plasma concentrations. If concomitant use is unavoidable, increase the starting dose of LORBRENA to 125 mg once daily.
- **Hepatic impairment:** No dose adjustments are recommended for patients with mild hepatic impairment. In a hepatic impairment study following administration of a single oral 100 mg dose of LORBRENA, lorlatinib exposure (AUC_{inf}) increased by 15% and 82% in patients with moderate hepatic impairment (Child-Pugh B) and severe hepatic impairment (Child-Pugh C), respectively, compared to subjects with normal hepatic function (see 10. Clinical Pharmacology). However, as lorlatinib exhibits net autoinduction at steady state in patients without hepatic impairment following repeated dosing, there are uncertainties associated with the applicability of single dose exposure results to steady state exposure in patients with hepatic impairment. Exposure in patients with moderate or severe hepatic impairment following multiple doses may be higher than those observed in the single dose study. If LORBRENA is used in patients with moderate or severe hepatic impairment, dose reductions should be considered and close monitoring is recommended.

- **Renal impairment:** No dose adjustment is needed for patients with mild or moderate impairment [absolute estimated glomerular filtration rate ≥ 30 mL/min). Reduce the dose when administering LORBRENA in patients with severe renal impairment (absolute eGFR < 30 mL/min) from 100 mg to 75 mg orally once daily (see 10. Clinical Pharmacology). Lorlatinb is not recommended for patients requiring hemodialysis as information for use in these patients is very limited.

4.2. Recommended Dose and Dosage Adjustment

Recommended Dose:

The recommended dose of LORBRENA is 100 mg taken orally once daily continuously. Continue treatment with LORBRENA until disease progression or unacceptable toxicity.

LORBRENA may be taken with or without food (see 10. Clinical Pharmacology).

Pediatric patients (<18 years):

The safety and efficacy of LORBRENA in pediatric patients have not been established. Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years):

No clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients (see 10. Clinical Pharmacology).

Dose Modifications:

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. Dose reduction levels are summarized below.

- First dose reduction: LORBRENA 75 mg taken orally once daily
- Second dose reduction: LORBRENA 50 mg taken orally once daily

LORBRENA should be permanently discontinued if the patient is unable to tolerate LORBRENA 50 mg taken orally once daily.

Dose modification recommendations for toxicities are provided in Table 1. Dose modification recommendations for patients who develop first-degree, second-degree, or complete atrioventricular (AV) block are provided in Table 2.

Table 1. LORBRENA Dose Modifications and Management Recommendations for Adverse Reactions

Adverse Reaction	LORBRENA Dosing
Hypercholesterolemia or Hypertriglyceridemia	
Mild hypercholesterolemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L) OR Mild hypertriglyceridemia (triglycerides between 150 and 300 mg/dL or 1.71 and 3.42 mmol/L)	Introduce or modify lipid-lowering therapy[a] in accordance with respective prescribing information; continue LORBRENA at same dose.
Moderate hypercholesterolemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L) OR Moderate hypertriglyceridemia (triglycerides between 301 and 500 mg/dL or 3.43 and 5.7mmol/L)	
Severe hypercholesterolemia (cholesterol between 401 and 500 mg/dL or between 10.35 and 12.92 mmol/L) OR Severe hypertriglyceridemia (triglycerides between 501 and 1000 mg/dL or 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy;[a] if currently on lipid-lowering therapy, increase the dose of this therapy[a] in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue LORBRENA at the same dose without interruption.
Grade 4 hypercholesterolemia (cholesterol over 500 mg/dL or over 12.92 mmol/L) OR Grade 4 hypertriglyceridemia (triglycerides over 1000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[a] or increase the dose of this therapy[a] in accordance with respective prescribing information or change to a new lipid-lowering therapy. Withhold LORBRENA until recovery of hypercholesterolemia and/or hypertriglyceridemia to moderate or mild severity grade. Re-challenge at same LORBRENA dose while maximizing lipid-lowering therapy[a] in accordance with respective prescribing information. If severe hypercholesterolemia and/or hypertriglyceridemia recurs despite maximal lipid-lowering therapy[a] in accordance with respective prescribing information, reduce LORBRENA by 1 dose level.

Adverse Reaction	LORBRENA Dosing
Central nervous system (CNS) effects[b,c]	
Grade 1: Mild	Continue at the same dose or withhold dose until recovery to baseline. Then resume LORBRENA at the same dose or reduce by 1 dose level.
Grade 2: Moderate OR Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume LORBRENA at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue LORBRENA.
Interstitial Lung Disease (ILD)/Pneumonitis	
Any Grade treatment–related ILD/Pneumonitis	Permanently discontinue LORBRENA.
Hypertension	
Grade 3 (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg; medical intervention indicated; more than one antihypertensive drug, or more intensive therapy than previously used indicated)	Withhold LORBRENA until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume LORBRENA at the same dose. If Grade 3 hypertension recurs, withhold LORBRENA until recovery to Grade 1 or less, and resume at a reduced dose. If adequate hypertension control cannot be achieved with optimal medical management, permanently discontinue LORBRENA.
Grade 4 (life-threatening consequences, urgent intervention indicated)	Withhold LORBRENA until recovery to Grade 1 or less, and resume at a reduced dose or permanently discontinue LORBRENA. If Grade 4 hypertension recurs, permanently discontinue LORBRENA.
Hyperglycemia	
Grade 3 (greater than 250 mg/dL) despite optimal anti-hyperglycemic therapy OR Grade 4	Withhold LORBRENA until hyperglycemia is adequately controlled, then resume LORBRENA at the next lower dosage. If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue LORBRENA.

Adverse Reaction	LORBRENA Dosing
Other adverse reactions[c]	
Grade 1 OR Grade 2	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3	Withhold LORBRENA until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume LORBRENA at 1 reduced dose level.

Abbreviations: CNS=central nervous system; CTCAE=Common Terminology Criteria for Adverse Events; HMG CoA=3-hydroxy-3-methylglutaryl coenzyme A; DBP=diastolic blood pressure; SBP= systolic blood pressure; ULN=upper limit of normal.

[a] Lipid-lowering therapy may include: HMG CoA reductase inhibitor, nicotinic acid, fibric acid, or ethyl esters of omega-3 fatty acids.

[b] Examples of CNS effects comprise psychotic effects (including hallucination) and changes in cognition, mood, mental status or speech (see 7. Warnings and Precautions and 8. Adverse Reactions).

[c] Grade categories are based on CTCAE classifications.

Table 2. Recommended LORBRENA Dose Modifications - PR Interval Prolongation/Atrioventricular Block

Event	LORBRENA Dosing	
	Asymptomatic	Symptomatic
First-degree AV block	Continue LORBRENA at the same dose without interruption. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely.	Withhold LORBRENA. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If symptoms resolve, resume LORBRENA at same dose or at 1 reduced dose level.
Second-degree AV block	Withhold LORBRENA. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If subsequent ECG does not show second-degree block, resume LORBRENA at same dose or 1 reduced dose level.	Withhold LORBRENA. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. 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

Event	LORBRENA Dosing	
	Asymptomatic	Symptomatic
		block, resume LORBRENA at 1 reduced dose level.
Complete AV Block	Withhold LORBRENA dose. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with AV block. If AV block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, may resume LORBRENA at full dose. If no pacemaker placed, resume LORBRENA at 1 reduced dose level only when symptoms resolve AND PR interval is less than 200 msec.	

Abbreviations: AV=atrioventricular; ECG=electrocardiogram.

4.4. Administration

Patients should be encouraged to take their dose of LORBRENA at approximately the same time each day. Tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

4.5. Missed Dose

If a dose of LORBRENA is missed, then it should be taken as soon as the patient remembers unless it is less than 4 hours before the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

5. Overdose

There is no known antidote for LORBRENA (lorlatinib). The treatment of LORBRENA overdose should consist of general supportive measures. Given the dose-dependent effect on PR interval, ECG monitoring is recommended.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral	Film-coated tablet 25 mg, 100 mg	Tablet core contains: dibasic calcium phosphate anhydrous, magnesium stearate, microcrystalline cellulose, sodium starch glycolate

		Film-coating contains: ferrosofferic oxide/Black iron oxide, hydroxypropyl methylcellulose (HPMC) 2910/hypromellose, iron oxide red, lactose monohydrate, macrogol/polyethylene glycol (PEG) 3350, titanium dioxide, triacetin

Description

25 mg: 8 mm round tan immediate release film-coated tablet, debossed with "Pfizer" on one side and "25" and "LLN" on the other side.

100 mg: oval (17 x 8.5 mm) lavender immediate release film-coated tablet, debossed with "Pfizer" on one side and "LLN 100" on the other side.

Packaging: LORBRENA is supplied as follows:

25 mg

- high density polyethylene bottles containing 30, 60, or 100 tablets
- aluminum foil blisters with aluminum foil backing containing 120 tablets (12 cards of 10 tablets)§

100 mg

- high density polyethylene bottles containing 30, 60, or 100 tablets
- aluminum foil blisters with aluminum foil backing containing 30 tablets (3 cards of 10 tablets)§

§ not commercially available in Canada

7. Warnings and Precautions

See 3. Serious Warnings and Precautions Box.

General

Patients treated with LORBRENA (lorlatinib) must have a documented ALK-positive status based on a validated ALK assay. Assessment of ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized.

Drug-Drug Interactions

Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers

Severe hepatotoxicity occurred in 10 of 12 healthy subjects receiving a single dose of LORBRENA with multiple daily doses of rifampin, a strong CYP3A inducer. Grade 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations occurred in 6 subjects (50%), Grade 3 ALT or AST elevations occurred in 4 subjects (33%) and Grade 2 ALT or AST elevations occurred in 1 subject (8%). ALT or AST elevations occurred within 3 days and returned to within normal limits after a median of 15 days (7 to 34 days); the median time to recovery was 18 days in subjects with Grade 3 or 4 ALT or AST elevations and 7 days in subjects with Grade 2 ALT or AST elevations.

No clinically meaningful changes in liver function tests were seen in healthy subjects after receiving a combination of lorlatinib with the moderate CYP3A inducer modafinil (see 9. Drug Interactions and 10. Clinical Pharmacology).

Carcinogenesis and Genotoxicity

Please see 16. Non-Clinical Toxicology.

Cardiovascular

Atrioventricular (AV) Block

PR interval prolongation and atrioventricular (AV) block events have been reported in patients receiving LORBRENA. In 476 patients who received 100 mg LORBRENA daily in Study B7461001 (n=327) and Study B7461006 (n=149) and who had a baseline electrocardiography (ECG), 9 patients (1.9%) experienced AV block and 1 patient (0.2%) experienced Grade 3 AV block and underwent pacemaker placement (see 10.2. Pharmacodynamics).

For those patients who develop AV block, dose modification may be required (see 4. Dosage and Administration).

Hypertension

Hypertension can occur in patients receiving LORBRENA (see 8. Adverse Reactions). Hypertension occurred in 62 patients (13%) who received 100 mg LORBRENA once daily in Study B7461001 and Study B7461006, including Grade 3 or 4 in 29 patients (6.1%). The median time to onset of hypertension was 6.4 months (1 day to 2.8 years), and 11 patients (2.3%) temporarily discontinued LORBRENA for hypertension.

Withhold and resume at a reduced dose or permanently discontinue LORBRENA based on severity (see 4. Dosage and Administration).

Driving and Operating Machinery

LORBRENA has moderate influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience central nervous system effects (see 8.2. Clinical Trial Adverse Reactions, Nervous system disorders).

Endocrine and Metabolism

Hyperlipidemia

The use of LORBRENA has been associated with increases in serum cholesterol and triglycerides (see 8. Adverse Reactions). Grade 3 or 4 elevations in total cholesterol occurred in 87 patients (18%) and Grade 3 or 4 elevations in triglycerides occurred in 92 patients (19%) of the 476 patients who received 100 mg LORBRENA once daily in Study B7461001 (n=327) and in Study B7461006 (n=149). The median time to onset for both hypercholesterolemia and hypertriglyceridemia was 15 days. The median duration of hypercholesterolemia and hypertriglyceridemia was 451 and 427 days, respectively. No patient was permanently discontinued from treatment with lorlatinib associated with hypercholesterolemia or hypertriglyceridemia. Eighteen (4%) and 33 (7%) patients required temporary discontinuation and 6 (1%) and 13 (3%) patients required dose reduction of LORBRENA for elevations in cholesterol and in

triglycerides in Study B7461001 and Study B7461006, respectively. Three hundred ninety-seven patients (83%) required initiation of lipid-lowering medications, with a median time to onset of start of such medications of 17 days.

Initiation, or increase in the dose, of lipid-lowering agents is recommended (see 4. Dosage and Administration).

Hyperglycemia

Hyperglycemia can occur in patients receiving LORBRENA (see 8. Adverse Reactions). Hyperglycemia occurred in 44 patients (9.2%) who received 100 mg LORBRENA once daily in Study B7461001 and Study B7461006, including Grade 3 or 4 in 15 patients (3.2%). The median time to onset of hyperglycemia was 4.8 months (1 day to 2.9 years), and 0.8% of patients temporarily discontinued LORBRENA for hyperglycemia.

Withhold and resume at a reduced dose or permanently discontinue LORBRENA based on severity (see 4. Dosage and Administration).

Monitoring and Laboratory Tests

ALK Testing

Patients treated with LORBRENA must have a documented ALK-positive status based on a validated ALK assay. Assessment of ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized.

Liver Function Tests

No clinically meaningful changes in liver function tests were seen in healthy subjects after receiving a combination of lorlatinib with the moderate CYP3A inducer modafinil (see 9. Drug Interactions and 10. Clinical Pharmacology).

Pancreatic enzymes - Lipase and amylase increase

Patients should be monitored for lipase and amylase elevations prior to the start of LORBRENA treatment and periodically thereafter as clinically indicated.

ECG Monitoring

Monitor ECG prior to initiating LORBRENA and monthly thereafter, particularly in patients with predisposing conditions to the occurrence of clinically significant cardiac events (see 7. Warnings and Precautions, Cardiovascular; 4. Dosage and Administration).

Hypertension

Control blood pressure prior to initiation of LORBRENA. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with LORBRENA. Withhold and resume at a reduced dose or permanently discontinue LORBRENA based on severity (see 7. Warnings and Precautions, Hypertension

, 4. Dosage and Administration).

Hyperlipidemia

Monitor serum cholesterol and triglycerides before initiating LORBRENA, 2, 4, and 8 weeks, after initiating LORBRENA, and periodically thereafter. Withhold and resume at the same dose for the first occurrence: resume at the same or a reduced dose of LORBRENA for recurrence based on severity (see 7. Warnings and Precautions, Endocrine and Metabolism; 4. Dosage and Administration; 8.2. Clinical Trial Adverse Reactions).

Hyperglycemia

Assess fasting serum glucose prior to initiation of LORBRENA and monitor periodically thereafter (see 7. Warnings and Precautions, Endocrine and Metabolism; 4. Dosage and Administration)

Neurologic

Central Nervous System Effects

Central nervous system (CNS) effects have been observed in patients receiving LORBRENA (see 8.2. Clinical Trial Adverse Reactions). These include seizures, psychotic effects and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep. Overall, CNS effects occurred in 246 (52%) of the 476 patients who received 100 mg LORBRENA once daily in clinical trials (see 8.2. Clinical Trial Adverse Reactions). Cognitive effects occurred in 132 (28%) of the 476 patients; in 14 patients (2.9%) these events were severe (Grade 3 or 4). Mood effects occurred in 102 patients (21%); in 8 patients (1.7%) these events were severe. Speech effects occurred in 50 patients (11%); in 3 patients (0.6%) these events were severe. Psychotic effects occurred in 33 patients (7%); in 3 patients (0.6%) these events were severe. Mental status changes occurred in 6 patients (1.3%); in 5 patients (1.1%) these events were severe. Seizures occurred in 9 patients (1.9%) patients, sometimes in conjunction with other neurologic findings. Sleep effects occurred in 55 patients (12%). The median time to first onset of any CNS effect was 1.4 months (1 day to 3.4 years). Overall, 10 patients (2.1%) required permanent discontinuation of LORBRENA for a CNS effect; 46 patients (10%) required temporary discontinuation and 36 patients (8%) required dose reduction.

Dose modification may be required for those patients who develop CNS effects. Permanent discontinuation of LORBRENA is recommended in patients diagnosed with Grade 4 CNS effects (see 4. Dosage and Administration).

Reproductive Health

Women of childbearing potential should be advised to avoid becoming pregnant while receiving LORBRENA. A highly effective non-hormonal method of contraception is required for female patients during treatment with LORBRENA because lorlatinib can render hormonal contraceptives ineffective (see 9. Drug Interactions). If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 21 days after completing therapy.

During treatment with LORBRENA and for at least 97 days after the final dose, advise male patients with female partners of reproductive potential to use effective contraception, including a condom, and advise male patients with pregnant partners to use condoms.

- **Fertility**

Based on nonclinical safety findings, male and female fertility may be compromised during treatment with LORBRENA (see 16. Non-Clinical Toxicology). It is not known whether LORBRENA affects female fertility. Men should seek advice on effective fertility preservation before treatment.

Respiratory

ILD/Pneumonitis

Severe or life-threatening pulmonary adverse reactions consistent with pneumonitis have occurred with LORBRENA. Pneumonitis occurred in 9 patients (1.9%) who received 100 mg LORBRENA once daily in Study B7461001 (n=327) and in Study B7461006 (n=149), including Grade 3 or 4 pneumonitis in 3 patients (0.6%). Four patients (0.8%) discontinued LORBRENA for ILD/pneumonitis.

Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever). Immediately withhold LORBRENA in patients with suspected ILD/pneumonitis. Permanently discontinue LORBRENA for treatment-related ILD/pneumonitis of any severity (see 4. Dosage and Administration).

7.1. Special Populations

7.1.1. Pregnancy

Studies in animals have shown embryo-fetal toxicity (see 16. Non-Clinical Toxicology). There are no data in pregnant women using LORBRENA. LORBRENA may cause fetal harm when administered to a pregnant woman.

LORBRENA is not recommended during pregnancy or for women of childbearing potential not using contraception.

7.1.2. Breastfeeding

It is not known whether lorlatinib and its metabolites are excreted in human milk. A risk to the newborn child cannot be excluded.

LORBRENA should not be used during breast-feeding. Breast-feeding should be discontinued during treatment with LORBRENA and for 7 days after the last dose.

7.1.3. Pediatrics

Pediatrics (<18 years of age): The safety and effectiveness of LORBRENA in the pediatric population were not established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Among patients from Study B7461001 who received 100 mg LORBRENA orally once daily (n=295), 241 patients were < 65 years and 54 patients were ≥65 years. Among patients from Study B7461006 who received 100 mg LORBRENA orally once daily (n=149), 90 patients were < 65 years and 59 patients

were ≥65 years. The following adverse events were more frequently reported in patients ≥65 years: cognitive effects, dyspnea, fatigue, arthralgia, diarrhea, anemia, myalgia, vomiting, back pain and rash. The limited data on the safety and efficacy of LORBRENA in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see 10. Clinical Pharmacology). No clinically relevant differences in safety or efficacy were observed between patients aged greater than or equal to 65 years and younger patients.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The pooled safety population described in the 7. Warnings and Precautions section reflects exposure to LORBRENA in 476 patients who received 100 mg LORBRENA once daily in Study B7461001 (N=327) and Study B7461006 (N=149). Among 476 patients who received LORBRENA, 75% were exposed for 6 months or longer and 61% were exposed for greater than 1 year. In this pooled safety population, the most frequent adverse reactions in ≥ 20% of 476 patients who received LORBRENA were edema (56%), peripheral neuropathy (44%), weight gain (31%), cognitive effects (28%), fatigue (27%), dyspnea (27%), arthralgia (24%), diarrhea (23%), mood effects (21%), and cough (21%). Temporary discontinuation occurred 245 (51.5%) of patients, dose reduction occurred in 117 (24.6%) of patients, and permanent discontinuation occurred in 44 (9.2%) of patients. The most frequent Grade 3-4 laboratory abnormalities in ≥ 20% of 476 patients who received LORBRENA were hypercholesterolemia (21%) and hypertriglyceridemia (21%).

Previously Untreated ALK-Positive Metastatic Non-Small Cell Lung Cancer (Phase 3 Study B7461006)

The safety of LORBRENA was evaluated in 149 patients with ALK-positive non-small cell lung cancer (NSCLC) in randomized, open-label, active-controlled Phase 3 Study B7461006. The median duration of exposure to LORBRENA was 16.7 months (4 days to 34.3 months) and 76% received LORBRENA for at least 12 months. Patient characteristics were: median age of 59 years (47 to 68 years), age ≥65 years (35%), female (59%), White (49%), Asian (44%), and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (96%).

The most frequent (≥20%) adverse reactions reported in patients treated with LORBRENA were edema, weight gain, peripheral neuropathy, cognitive effects, diarrhea, and dyspnea. Of the worsening laboratory values, the most frequent (≥30%) were hypertriglyceridemia, hypercholesterolemia, increased creatinine, increased gamma glutamyl transferase (GGT), increased AST, hyperglycemia, increased ALT, increased creatine phosphokinase (CPK), hypoalbuminemia, and anemia.

Serious adverse reactions occurred in 51 (34%) of the 149 patients treated with LORBRENA; the most frequently reported serious adverse reactions were pneumonia in 7 patients (4.7%), dyspnea in 4 patients (2.7%), respiratory failure in 4 patients (2.7%), cognitive effects in 3 patients (2.0%), and pyrexia in 3 patients (2.0%).

Fatal adverse reactions occurred in 7 (4.7%) of patients treated with LORBRENA and included pneumonia in 1 patient (0.7%), respiratory failure in 1 patient (0.7%), cardiac failure acute in 1 patient (0.7%), disease progression in 1 patient (0.7%), lung neoplasm malignant in 1 patient (0.7%), pulmonary embolism in 1 patient (0.7%), and death in 1 patient (0.7%).

Permanent discontinuation of LORBRENA due to adverse reactions occurred in 10 (6.7%) patients. The most frequent adverse reactions that led to permanent discontinuation of LORBRENA was cognitive

effects in 2 patients (1.3%). Dose interruption was required in 73 (49%) patients treated with LORBRENA. The most frequent adverse reactions that led to dose interruptions of LORBRENA were hypertriglyceridemia in 11 patients (7.4%), edema in 8 patients (5.4%), pneumonia in 7 patients (4.7%), cognitive effects in 6 patients (4.0%), hypercholesterolemia in 5 patients (3.4%), and mood effects in 5 patients (3.4%). At least 1 dose reduction due to adverse reactions was required in 31 (21%) patients. The most frequent adverse reactions that led to dose reductions were edema in 8 patients (5.4%), hypertriglyceridemia in 6 patients (4.0%), and peripheral neuropathy in 5 patients (3.4%).

Previously Treated ALK-Positive Metastatic NSCLC (Phase 1/2 Study B7461001)

The data from B7461001 described below reflect exposure to LORBRENA in 295 adult patients with ALK positive or ROS1 positive metastatic NSCLC who received LORBRENA 100 mg orally once daily in Study B7461001. The majority of subjects (232 subjects, 78.6%) had been previously treated with 1 or more ALK or ROS1 TKIs.

The median duration of treatment was 12.5 months (range: 1 day to 35 months), the median age was 53 years (range: 19 to 85 years), and 18% of patients were older than 65 years. A total of 170 patients (58%) were female, 145 patients (49%) were White, and 108 patients (37%) were Asian.

The most frequent (≥ 20%) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight increased, arthralgia, mood effects and diarrhea.

Of the worsening laboratory values occurring in ≥ 20% of patients, the most frequent were hypercholesterolemia, hypertriglyceridemia, anemia, hyperglycemia, increased AST, hypoalbuminemia, increased ALT, lipase increased, and increased alkaline phosphatase.

Serious adverse reactions occurred in 95 (32%) of the 295 patients; the most frequently reported serious adverse reactions were pneumonia in 10 patients (3.4%), dyspnea in 8 patients (2.7%), pyrexia in 6 patients (2%), mental status changes in 4 patients (1.4%), and respiratory failure in 4 patients (1.4%). Fatal adverse reactions occurred in 8 patients (2.7%) and included pneumonia in 2 patients (0.7%), myocardial infarction in 2 patients (0.7%), acute pulmonary edema in 1 patient (0.3%), embolism in 1 patient (0.3%), peripheral artery occlusion in 1 patient (0.3%), and respiratory distress in 1 patient (0.3%). Permanent discontinuation of LORBRENA for adverse reactions occurred in 23 patients (8%).

The most frequent adverse reactions that led to permanent discontinuation were respiratory failure in 4 patients (1.4%), dyspnea in 2 patients (0.7%), myocardial infarction in 2 patients (0.7%), cognitive effects in 2 patients (0.7%) and mood effects in 2 patients (0.7%). Dose interruption was required in 142 patients (48%). The most frequent adverse reactions that led to dose interruptions were edema in 20 patients (7%), hypertriglyceridemia in 17 patients (6%), peripheral neuropathy in 15 patients (5%), cognitive effects in 13 patients (4.4%), increased lipase in 11 patients (3.7%), hypercholesterolemia in 10 patients (3.4%), mood effects in 9 patients (3.1%), dyspnea in 8 patients (2.7%), pneumonia in 8 patients (2.7%), and hypertension in 6 patients (2.0%). At least 1 dose reduction due to adverse reactions was required in 71 patients (24%). The most frequent adverse reactions that led to dose reductions were edema in 18 patients (6%), peripheral neuropathy in 14 patients (4.7%), cognitive effects in 12 patients (4.1%), and mood effects in 9 patients (3.1%).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in the clinical trials of another drug.

Table 3 summarizes the most frequent adverse reactions in patients treated with LORBRENA in the Phase 3 study.

Table 3. Adverse Reactions (≥10% for all NCI CTCAE Grades or ≥2% for Grades 3-4) in Patients Treated with LORBRENA in Phase 3 Study B7461006*

Adverse Reaction	LORBRENA n=149		Crizotinib n=142	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Psychiatric				
Mood effects[a]	24 (16.1)	2 (1.3)	7 (4.9)	0
Nervous system				
Peripheral neuropathy[b]	50 (33.6)	3 (2.0)	21 (14.8)	1 (0.7)
Cognitive effects[c]	32 (21.5)	3 (2.0)	8 (5.6)	0
Headache	25 (16.8)	0	25 (17.6)	1 (0.7)
Dizziness	16 (10.7)	0	20 (14.1)	0
Sleep effects[d]	17 (11.4)	2 (1.3)	14 (9.9)	0
Respiratory				
Dyspnea	30 (20.1)	4 (2.7)	23 (16.2)	3 (2.1)
Cough	24 (16.1)	0	26 (18.3)	0
Respiratory failure	4 (2.7)	3 (2.0)	0	0
Vascular disorders				
Hypertension	27 (18.1)	15 (10.1)	3 (2.1)	0
Ocular				
Vision disorder[e]	27 (18.1)	0	56 (39.4)	1 (0.7)
Gastrointestinal				
Diarrhea	32 (21.5)	2 (1.3)	74 (52.1)	1 (0.7)
Nausea	22 (14.8)	1 (0.7)	74 (52.1)	3 (2.1)
Constipation	26 (17.4)	0	42 (29.6)	1 (0.7)
Vomiting	19 (12.8)	1 (0.7)	55 (38.7)	2 (1.4)
Musculoskeletal and connective tissue	28 (18.8)	1 (0.7)	16 (11.3)	0
Arthralgia	23 (15.4)	1 (0.7)	10 (7.0)	0
Myalgia[f]				

Adverse Reaction	LORBRENA n=149		Crizotinib n=142	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Back pain	22 (14.8)	1 (0.7)	16 (11.3)	0
Pain in extremity	26 (17.4)	0	12 (8.5)	0
General				
Edema[g]	83 (55.7)	6 (4.0)	57 (40.1)	2 (1.4)
Weight gain	57 (38.3)	25 (16.8)	18 (12.7)	3 (2.1)
Fatigue[h]	29 (19.5)	2 (1.3)	46 (32.4)	4 (2.8)
Pyrexia	25 (16.8)	2 (1.3)	18 (12.7)	2 (1.4)
Chest pain	16 (10.7)	2 (1.3)	20 (14.1)	1 (0.7)
Infections				
Upper respiratory tract infection[i]	17 (11.4)	1 (0.7)	11 (7.7)	2 (1.4)
Pneumonia	11 (7.4)	3 (2.0)	12 (8.5)	5 (3.5)
Bronchitis	10 (6.7)	3 (2.0)	3 (2.1)	0
Skin				
Rash[j]	17 (11.4)	0	12 (8.5)	0

* Adverse reactions were graded using NCI CTCAE version 4.03.

Abbreviations: NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SOC=System organ class.

[a] Mood effects (including affective disorder, affect lability, agitation, anger, anxiety, bipolar I disorder, depressed mood, depression, depressive symptom, euphoric mood, intentional self-injury, irritability, mood altered, mood swings, stress).

[b] Peripheral neuropathy (including dysesthesia, gait disturbance, hypoesthesia, motor dysfunction, muscular weakness, neuralgia, neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy).

[c] Cognitive effects (including events from SOC Nervous system disorders: amnesia, cognitive disorder, disturbance in attention, memory impairment, mental impairment; and also including events from SOC Psychiatric disorders: confusional state, delirium, disorientation).

[d] Sleep effects (including insomnia, nightmare, sleep disorder, somnambulism).

[e] Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).

[f] Myalgia (including musculoskeletal pain, myalgia).

Adverse Reaction	LORBRENA n=149		Crizotinib n=142	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
[g] Edema (including edema, edema peripheral, eyelid edema, face edema, generalized edema, localized edema, periorbital edema, peripheral swelling, swelling). [h] Fatigue (including asthenia, fatigue). [i] Upper respiratory tract infection (including upper respiratory infection). [j] Rash (including dermatitis acneiform, maculopapular rash, rash).				

Table 4 summarizes the most frequent adverse reactions in patients treated with LORBRENA in the Phase 1/2 Study B7461001.

Table 4. Adverse Reactions Reported in ≥ 10% of Patients in Phase 1/2 Study B7461001*

Adverse Reaction	LORBRENA (N=295)	
	All Grades n (%)	Grade 3-4 n (%)
Metabolism and nutrition disorders		
Hypercholesterolemia[a]	249 (84.4)	49 (16.6)
Hypertriglyceridemia[b]	197 (66.8)	48 (16.3)
Psychiatric disorders		
Mood effects[c]	65 (22.0)	5 (1.7)
Nervous system disorders		
Peripheral neuropathy[d]	140 (47.5)	8 (2.7)
Cognitive effects[e]	80 (27.1)	6 (2.0)
Headache	52 (17.6)	2 (0.7)
Dizziness	48 (16.3)	2 (0.7)
Speech effects[f]	34 (11.5)	1 (0.3)
Sleep effects[g]	29 (9.8)	0
Respiratory		
Dyspnea	79 (26.8)	16 (5.4)
Cough	54 (18.3)	0
Eye disorders		
Vision disorder[h]	43 (14.6)	1 (0.3)
Gastrointestinal disorders		
Diarrhea	64 (21.7)	2 (0.7)
Nausea	52 (17.6)	2 (0.7)
Constipation	45 (15.3)	0
Vomiting	34 (11.5)	3 (1.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	67 (22.7)	2 (0.7)
Myalgia[i]	50 (16.9)	0
Back pain	38 (12.9)	2 (0.7)
Pain in extremity	39 (13.2)	1 (0.3)
General disorders and administration site conditions		
Edema[j]	159 (53.9)	7 (2.4)
Fatigue[k]	76 (25.8)	1 (0.3)
	36 (12.2)	2 (0.7)

Adverse Reaction	LORBRENA (N=295)	
	All Grades n (%)	Grade 3-4 n (%)
Pyrexia		
Infections Upper respiratory tract infection[l]	36 (12.2)	0
Skin and subcutaneous tissue disorders Rash[m]	41 (13.9)	1 (0.3)
Investigations Weight increased	71 (24.1)	13 (4.4)

* Adverse reactions were graded using NCI CTCAE version 4.0.

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. Terms actually reported in the studies up to the data cutoff date and contributing to the relevant adverse reaction are indicated in parentheses, as listed below.

Abbreviations: NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

[a] Hypercholesterolemia (including blood cholesterol increased, hypercholesterolemia).

[b] Hypertriglyceridemia including (blood triglycerides increased, hypertriglyceridemia).

[c] Mood effects (including affective disorder, affect lability, aggression, agitation, anxiety, depressed mood, depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress, suicidal ideation).

[d] Peripheral neuropathy (including burning sensation, carpal tunnel syndrome, dysesthesia, formication, gait disturbance, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral sensory neuropathy, sensory disturbance).

[e] Cognitive effects (including events from SOC Nervous system disorders: amnesia, cognitive disorder, dementia, disturbance in attention, memory impairment, mental impairment; and also including events from SOC Psychiatric disorders: attention deficit/hyperactivity disorder, confusional state, delirium, reading disorder).

[f] Speech effects (including aphasia, dysarthria, slow speech, speech disorder)

[g] Sleep effects (including abnormal dreams, insomnia, nightmare, sleep disorder, sleep talking, somnambulism)

[h] Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).

[l] Myalgia (including musculoskeletal pain, myalgia).

[j] Edema (including edema, edema peripheral, eyelid edema, face edema, generalized edema, localized edema, periorbital edema, peripheral swelling, swelling).

[k] Fatigue (including asthenia, fatigue).

[l] Upper respiratory infection (including fungal upper respiratory infection, upper respiratory infection, viral upper respiratory infection).

[m] Rash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash).

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

The safety of lorlatinib has not been demonstrated in pediatric population. Preliminary phase 1 study of lorlatinib as a single agent and in combination with chemotherapy in pediatric, adolescent, and adult patients with ALK aberrant relapsed or refractory high-risk neuroblastoma (HR NBL) is ongoing.

8.3. Less Common Clinical Trial Adverse Reactions

In Study B7461006, additional clinically significant adverse reactions occurring at an overall incidence between 1% and 10% in patients treated with LORBRENA included speech effects in 10 patients (6.7%) and psychotic effects in 5 patients (3.4%).

In Study B7461001, additional clinically significant adverse reactions occurring at an overall incidence between 1% and 10% in patients treated with LORBRENA included psychotic effects in 21 patients (7%).

8.3.1. Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 5 summarizes laboratory abnormalities in patients treated with LORBRENA in Phase 3 study B7461006.

Table 5. Worsening Laboratory Values Occurring in ≥20% of Patients in Phase 3 Study B7461006*

Laboratory Abnormality	LORBRENA n=149		Crizotinib n=142	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Chemistry				
Hypertriglyceridemia[a,A]	142 (95)	33 (22)	38 (27)	0
Hypercholesterolemia[a,A]	136 (91)	29 (19)	17 (12)	0
Increased creatinine[a,A]	121 (81)	1 (0.7)	139 (99)	3 (2.1)
Increased GGT[a,A]	77 (52)	9 (6.0)	58 (41)	9 (6.4)
Increased AST[a,A]	71 (48)	3 (2.0)	105 (75)	5 (3.5)
Hyperglycemia[a,A]	71 (48)	10 (6.7)	38 (27)	3 (2.1)
Increased ALT[a,A]	65 (44)	4 (2.7)	105 (75)	6 (4.3)
Increased CPK[a,A]	58 (39)	3 (2.0)	90 (64)	7 (5.0)
Hypoalbuminemia[a,A]	53 (36)	1 (0.7)	86 (61.0)	9 (6.4)
Increased lipase[a,A]	42 (28.2)	11 (7.4)	48 (34)	7 (5.0)
Increased alkaline phosphatase[a,A]	35 (23)	0	70 (50)	1 (0.7)
Hyperkalemia[a,A]	32 (21)	2 (1.3)	38 (27)	3 (2.1)
Increased amylase[b,A]	30 (20)	2 (1.4)	45 (32)	2 (1.4)
Hematology				
Anemia[a,A]	72 (48)	3 (2.0)	54 (38)	4 (2.8)
Activated PTT[c,B]	35 (25)	0	19 (14)	0
Lymphopenia[a,A]	34 (23)	4 (2.7)	61 (43)	8 (5.7)
Thrombocytopenia[a,A]	34 (23)	0	10 (7.1)	1 (0.7)

* Grades using NCI CTCAE version 4.03.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; GGT=gamma glutamyl transferase; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PTT=partial thromboplastin time.

N=number of patients who had at least one on-study assessment for the parameter of interest.

[a] N=149 (LORBRENA).

[A] N=141 (crizotinib).

[b] N=148 (LORBRENA).

[B] N=135 (crizotinib).

[c] N=138 (LORBRENA).

Table 6 summarizes laboratory abnormalities in patients treated with LORBRENA in Phase 1/2 Study B7461001.

Table 6. Worsening Laboratory Values Occurring in ≥20% of Patients in Phase 1/2 Study B7461001*

Laboratory Abnormality	LORBRENA	
	All Grades n (%)	Grade 3 or 4 n (%)
Chemistry		
Hypercholesterolemia[a]	279 (96)	52 (18)
Hypertriglyceridemia[a]	262 (90)	52 (18)
Hyperglycemia[b]	151 (52)	15 (5)
Increased AST[a]	108 (37)	6 (2.1)
Hypoalbuminemia[c]	95 (33)	3 (1.0)
Increased ALT[a]	82 (28)	6 (2.1)
Increased lipase[d]	70 (24)	28 (10)
Increased alkaline phosphatase[a]	70 (24)	3 (1.0)
Increased amylase[e]	61 (22)	11 (3.9)
Hypophosphatemia[a]	61 (21)	14 (4.8)
Hyperkalemia[b]	61 (21)	3 (1.0)
Hypomagnesemia[a]	60 (21)	0
Hematology		
Anemia[b]	152 (52)	14 (4.8)
Thrombocytopenia[b]	67 (23)	1 (0.3)
Lymphopenia[a]	63 (22)	10 (3.4)

* Grades using NCI CTCAE version 4.0.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

N=number of patients who had at least one on-study assessment for the parameter of interest.

[a] N=292.

[b] N=293.

[c] N=291.

[d] N=290.

[e] N=284.

8.5. Post-Market Adverse Reactions

Not applicable.

9. Drug Interactions

9.2. Drug Interactions Overview

In vitro data indicate that LORBRENA (lorlatinib) is primarily metabolized by CYP3A4 and uridine diphosphate-glucuronosyltransferase (UGT) 1A4, with minor contributions from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.

9.4. Drug-Drug Interactions

CYP3A inhibitors

Itraconazole, a strong inhibitor of CYP3A, administered at a dose of 200 mg once daily for 5 days, increased the mean area under the curve (AUC) by 42% and C_{max} by 24% of a single 100 mg oral dose of lorlatinib in healthy volunteers. Concomitant administration of lorlatinib with strong CYP3A inhibitors (e.g., boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, telaprevir, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either danoprevir, elvitegravir, indinavir, lopinavir, saquinavir, or tipranavir) may increase lorlatinib plasma concentrations. Grapefruit products may also increase lorlatinib plasma concentrations. Concomitant use with a strong CYP3A inhibitor increased lorlatinib plasma concentrations, which may increase the incidence and severity of adverse reactions of LORBRENA. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered. If a strong CYP3A inhibitor must be concomitantly administered, a dose reduction of lorlatinib is recommended (see 4. Dosage and Administration). Based on PBPK simulations, concomitant use of LORBRENA with fluconazole may increase lorlatinib plasma concentrations, which may increase the incidence and severity of adverse reactions of LORBRENA. Avoid concomitant use of LORBRENA with fluconazole. If concomitant use cannot be avoided, reduce the LORBRENA starting dose to 75 mg once daily.

CYP3A inducers
Rifampin, a strong inducer of CYP3A, administered at a dose of 600 mg once daily for 9 days, reduced the mean lorlatinib AUC by 85% and C_{max} by 76% of a single 100-mg dose of lorlatinib in healthy volunteers; increases in liver function tests (AST and ALT) were also observed. Concomitant administration of lorlatinib with strong CYP3A inducers (e.g., rifampin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's wort) may decrease lorlatinib plasma concentrations. Severe hepatotoxicity occurred in healthy subjects receiving LORBRENA with rifampin, a strong CYP3A inducer. The use of a strong CYP3A inducer with lorlatinib is contraindicated (see 2. Contraindications and 4. Dosage and Administration). Any strong CYP3A inducers have to be discontinued for at least 3 plasma half-lives of the strong CYP3A inducer before lorlatinib treatment is started. No clinically meaningful changes in liver function test results were seen after administration of the combination of a single 100 mg oral dose of lorlatinib with the moderate CYP3A inducer, modafinil (400 mg once daily for 19 days) in healthy volunteers. Concomitant use of lorlatinib with a moderate CYP3A inducer decreased lorlatinib plasma AUC by 23% and decreased C_{max} by 22% (see 10. Clinical Pharmacology). If concomitant use cannot be avoided, increase LORBRENA starting dose to 125 mg once daily.

Proton Pump inhibitors, H2-receptor antagonists, or locally acting antacids
The proton-pump inhibitor rabeprazole had a minimal effect on lorlatinib plasma exposure (90% CI for the AUC_{inf} ratio, expressed as a percentage: 97.6%, 104.3%).

No dose adjustment is required when lorlatinib is taken with proton-pump inhibitors, H2-receptor antagonists, or locally acting antacids.

Drugs whose plasma concentrations may be altered by lorlatinib:

CYP3A substrates
Lorlatinib has a net induction effect on CYP3A both in vitro and in vivo. Lorlatinib 150 mg orally once daily for 15 days decreased AUCinf by 64% and Cmax by 50% of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate). Concurrent administration of lorlatinib in patients resulted in decreased mean oral midazolam AUC and Cmax than that observed when midazolam was administered alone, suggesting that lorlatinib is an inducer of CYP3A. Thus, coadministration of lorlatinib with CYP3A substrates with narrow therapeutic indices, including but not limited to hormonal contraceptives, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, should be avoided since the concentration of these drugs may be reduced by lorlatinib.

In vitro studies of other CYP inhibition and induction
In vitro studies indicated that clinical drug-drug interactions as a result of lorlatinib mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 are unlikely to occur.

In vitro, studies indicated that lorlatinib is an inhibitor of CYP2C9 and that it activates the human pregnane X receptor (PXR), with the net effect *in vivo* being weak CYP2C9 induction. In vitro studies also indicated that lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A, with the net effect in vivo being induction. In vitro studies also indicated that lorlatinib is an inducer of CYP2B6 and activates the human constitutive androstane receptor (CAR), and in vivo lorlatinib is a weak inducer of CYP2B6. Therefore, concomitant use of lorlatinib with CYP2B6 substrates (e.g., bupropion, efavirenz) may result in reduced plasma concentrations of the CYP2B6 substrate. In vitro, lorlatinib has a low potential to cause drug-drug interactions by induction of CYP1A2.

In vitro, the major circulating metabolite for lorlatinib showed a low potential to cause drug-drug interaction by inhibiting CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, or by inducing CYP1A2, CYP2B6, and CYP3A.

In vitro studies of UDP-glucuronysyltransferase (UGT) inhibition
In vitro studies indicated that clinical drug-drug interactions as a result of lorlatinib mediated inhibition of the metabolism of substrates for UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15 are unlikely to occur. In vitro studies indicated that lorlatinib is an inhibitor of UGT1A1 and that it activates PXR, with the net effect in vivo being weak UGT induction.

In vitro studies indicated that clinical drug-drug interactions as a result of inhibition by the major lorlatinib circulating metabolite of substrates for UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 are unlikely to occur.

In vitro studies with drug transporters

In vitro studies indicated that clinical drug-drug interactions as a result of lorlatinib mediated inhibition of breast cancer resistance protein (BCRP, systemically), organic anion transporting polypeptide (OATP)1B1, OATP1B3, multidrug and toxin extrusion protein (MATE)2K, organic anion transporter (OAT)1, and organic cation transporter (OCT)2 are unlikely. In vitro studies indicated that lorlatinib is an inhibitor of P-glycoprotein (P-gp) and that it activates PXR, with the net effect in vivo being moderate P-gp induction. Lorlatinib may have the potential to inhibit P glycoprotein (P-gp, systemically and at the gastrointestinal [GI] tract), BCRP (GI tract), OCT1, MATE1, and OAT3 at clinically relevant concentrations.

In vitro studies indicated that clinical drug-drug interactions as a result of inhibition by the major lorlatinib circulating metabolite of substrates for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K are unlikely to occur.

In vivo studies with drug transporters

A drug interaction study conducted in non-small cell lung cancer patients indicated that lorlatinib is a moderate inducer of P gp. P-gp substrates with narrow therapeutic index (e.g., digoxin) should be used with caution in combination with lorlatinib due to the likelihood of reduced plasma concentrations of these substrates.

9.5. Drug-Food Interactions

Lorlatinib can be taken with or without food. Administration of lorlatinib with a high fat, high calorie meal resulted in 5% higher AUC_{inf} and 9% lower C_{max} (AUC_{inf} ratio of 104.7%; 90% CI for the ratio: 101.3%, 108.3%; C_{max} ratio of 90.89%; 90% CI for the ratio: 84.82%, 97.40%), compared to overnight fasting. However, taking lorlatinib with foods that are strong CYP3A inhibitors (e.g. Grapefruit products) may increase lorlatinib plasma concentrations and should be avoided.

9.6. Drug-Herb Interactions

Co-administration of lorlatinib with herbal products that are strong CYP3A inducers (e.g. St. John's wort) may decrease lorlatinib plasma concentrations. The use of a strong CYP3A inducer with lorlatinib is contraindicated (see 2. Contraindications and 4. Dosage and Administration). Avoid concomitant use with herbal products that are moderate CYP3A inducers, if possible, as they may also reduce lorlatinib plasma concentrations.

10. Clinical Pharmacology

10.1. Mechanism of Action

Lorlatinib is a selective, adenosine triphosphate (ATP) competitive, brain-penetrant, small molecule inhibitor of ALK and ROS1 tyrosine kinases that addresses mechanisms of resistance following previous treatment with ALK inhibitor therapy.

10.2. Pharmacodynamics

In nonclinical studies, lorlatinib potently inhibited catalytic activities of non-mutated ALK and a broad range of clinically relevant ALK mutant kinases in recombinant enzyme and cell-based assays. The ALK mutations analyzed included those conferring resistance to other ALK inhibitors.

Lorlatinib demonstrated marked antitumor activity at low nanomolar free plasma concentrations in mice bearing tumor xenografts that express echinoderm microtubule-associated protein-like 4 (EML4) fusions with ALK variant 1 (v1), including ALK mutations L1196M, G1269A, G1202R, and I1171T. Two of these ALK mutants, G1202R and I1171T, are known to confer resistance to first and second generation ALK inhibitors. Lorlatinib is also capable of penetrating the blood-brain barrier and achieved efficacious brain exposure in mice and rat. In mice bearing orthotropic EML4-ALK or EML4-ALK^{L1196M} brain tumor implants, lorlatinib caused tumor shrinkage and prolonged survival. The overall antitumor efficacy of lorlatinib was dose-dependent and correlated with inhibition of ALK phosphorylation.

Cardiac electrophysiology

QT interval

In B7461001, 2 patients (0.7%) had absolute Fridericia's correction QTc (QTcF) values >500 msec, and 5 patients (1.8%) had a change in QTcF from baseline >60 msec.

In addition, the effect of a single oral dose of lorlatinib (50 mg, 75 mg, and 100 mg) with and without 200 mg once daily itraconazole was evaluated in a 2-way crossover study in 16 healthy volunteers. No increases in the mean QTc interval were observed at the mean observed lorlatinib concentrations in this study.

PR interval

In 295 patients who received lorlatinib at the recommended dose of 100 mg once daily and had a ECG measurement in Study B7461001, the maximum mean change from baseline for PR interval was 16.4 ms (90% CI: 13.4, 19.4 ms). Among the 284 patients with PR interval <200 ms, 14% (40 patients) had PR interval prolongation ≥200 ms after starting lorlatinib. The prolongation of PR interval occurred in a concentration dependent manner. Atrioventricular block occurred in 1.0% of patients.

For those patients who develop PR prolongation, dose modification may be required (see 4. Dosage and Administration).

10.3. Pharmacokinetics

Absorption

In patients with cancer, peak lorlatinib concentrations in plasma are rapidly reached with the median T_{max} of 1.2hours following a single 100 mg dose and 2.0 hours following 100 mg once daily multiple dosing.

After oral administration of lorlatinib tablets, the mean absolute bioavailability is 80.8% (90% CI: 75.7%, 86.2%) compared to intravenous administration.

Administration of lorlatinib with a high fat, high calorie meal resulted in 5% higher AUC_{inf} and 9% lower C_{max} (AUC_{inf} ratio of 104.7%; 90% CI for the ratio: 101.3%, 108.3%; C_{max} ratio of 90.89%; 90% CI for the ratio: 84.82%, 97.40%), compared to overnight fasting. Lorlatinib may be administered with or without food. The proton pump inhibitor rabeprazole had a minimal effect on lorlatinib plasma exposure (AUC_{inf} ratio of 100.9%; 90% CI for the ratio: 97.6%, 104.3%). No dose adjustment is recommended when lorlatinib is taken with proton pump inhibitors, H2 receptor antagonists or locally acting antacids.

After multiple QD dose administration, lorlatinib C_{max} increased dose-proportionally and AUC_{tau} increased slightly less than dose-proportionally over the dose range of 10 mg to 200 mg QD.

At the 100 mg once daily lorlatinib dose, the Cycle 1 Day 15 geometric mean (geometric %CV) peak plasma concentration was 577 (42 ng/mL and the AUC_{24} 5650 (39) ng·h/mL in patients with cancer. The geometric mean (geometric %CV) oral clearance was 17.7 (39) L/h.

Distribution

In vitro binding of lorlatinib to human plasma proteins is 66% with moderate binding to both albumin and α1-acid glycoprotein.

The geometric mean (geometric %CV) steady state volume of distribution (Vss) of lorlatinib was 305 (28) L following 50 mg IV administration to healthy subjects. In patients with cancer, the geometric mean (geometric %CV) Vz/F after 100 mg single dose was 352 (37) L.

Metabolism

In humans, lorlatinib undergoes oxidation and glucuronidation as the primary metabolic pathways. In vitro data indicate that lorlatinib is metabolized primarily by CYP3A4 and UGT1A4, with minor contribution from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.

In plasma, a benzoic acid metabolite of lorlatinib resulting from the oxidative cleavage of the amide and aromatic ether bonds of lorlatinib was observed as a major metabolite, accounting for 21% of the circulating radioactivity. The oxidative cleavage metabolite is pharmacologically inactive.

Elimination

In patients with cancer, the plasma half life of lorlatinib after a single 100 mg dose was 23.6 hours. At steady state, lorlatinib plasma exposures are lower than those expected from single dose pharmacokinetics, indicating a net auto induction effect on lorlatinib metabolism. Following oral administration of a 100 mg radiolabeled dose of lorlatinib, a mean 47.7% of the radioactivity was recovered in urine and 40.9% of the radioactivity was recovered in feces, with overall mean total recovery of 88.6%.

Unchanged lorlatinib was the major component of human plasma and feces, accounting for 44% and 9.1% of total radioactivity in plasma and feces, respectively. Less than 1% of unchanged lorlatinib was detected in urine.

Special populations and conditions

- **Pediatrics** The safety and efficacy of LORBRENA (lorlatinib) in pediatric patients have not been established. Preliminary pharmacokinetic evaluations are ongoing based on a phase 1 study of lorlatinib as a single agent and in combination with chemotherapy in pediatric, adolescent, and adult patients with ALK aberrant relapsed or refractory high-risk neuroblastoma (HR NBL).
- **Geriatrics** Out of the 476 patients who received lorlatinib 100 mg orally once daily in Study B7461001 (N=327) and Study B7461006 (N=149), 25.5% of patients were aged 65 years or older. Of the 215 patients in the efficacy population in Study B7461001, 17.7% of patients were aged 65 years or older, and of the 149 patients in the lorlatinib arm of Study B7461006, 40% were aged 65 years or older. No clinically relevant differences in safety or efficacy were observed between patients aged greater than or equal to 65 years of age and younger patients (see 4. Dosage and Administration).
- **Age, gender, race, body weight, and phenotype:** Population pharmacokinetic analyses in patients with advanced NSCLC and healthy volunteers indicate that there are no clinically relevant effects of age, gender, race, body weight, or phenotypes for CYP3A5 and CYP2C19.
- **Hepatic Insufficiency** As lorlatinib is metabolized in the liver, hepatic impairment is likely to increase lorlatinib plasma concentrations. Clinical studies that were conducted excluded patients with AST or ALT >2.5 × ULN, or if due to underlying malignancy, >5.0 × ULN or with total bilirubin >1.5 × ULN. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild hepatic impairment (n=50). No dose adjustments are recommended for patients with mild hepatic impairment (see 4. Dosage and Administration). In a hepatic impairment study following administration of a single oral 100 mg dose of LORBRENA, lorlatinib AUC_{inf} increased by 15% and 82% in patients with moderate hepatic impairment (Child-Pugh B) and severe hepatic impairment (Child-Pugh C), respectively, compared to subjects with normal hepatic function. However, as lorlatinib exhibits net autoinduction at steady state in patients without hepatic impairment, there are uncertainties associated with the applicability of single dose exposure results to steady state exposure in patients with hepatic impairment. Exposure in patients with moderate and severe hepatic impairment compared to that of patients with normal hepatic function following multiple doses may be higher than those observed in the single dose study. Dose reductions should be considered in patients with moderate and severe hepatic impairment. Close monitoring is recommended (see 4. Dosage and Administration, 4.1 Dosing Considerations).
- **Renal Insufficiency** Less than 1% of the administered dose is detected unchanged lorlatinib in urine. Clinical studies excluded patients with serum creatinine >1.5 × ULN or estimated CL_{cr} <60 mL/min. Population pharmacokinetic analyses have shown that lorlatinib steady state exposure was not clinically meaningfully altered in patients with mild (n=103, CL_{cr}: 60-89 mL/min) or moderate renal impairment (n=41, CL_{cr}: 30-59 mL/min). Based on a renal impairment study, no dose adjustments are recommended for patients with mild or moderate renal impairment [absolute eGFR based on Modification of Diet in Renal Disease Study equation (MDRD)-derived eGFR (in mL/min/1.73 m2) × measured body surface area/1.73 ≥30 mL/min]. In

this study, lorlatinib AUC_{inf} increased by 41% in subjects with severe renal impairment (absolute eGFR<30 mL/min) compared to subjects with normal renal function (absolute eGFR≥90 mL/min). Reduce the recommended dosage of LORBRENA in patients with severe renal impairment, from 100 mg to 75 mg orally once daily (see 4. Dosage and Administration). The pharmacokinetics of lorlatinib have not been studied in patients with severe renal impairment requiring hemodialysis.

11. Storage, Stability, and Disposal

Store at 15°C to 30°C in the original package to protect from light.

12. Special Handling Instructions

LORBRENA does not require any special handling instructions.

Part 2: Scientific Information

13. Pharmaceutical Information

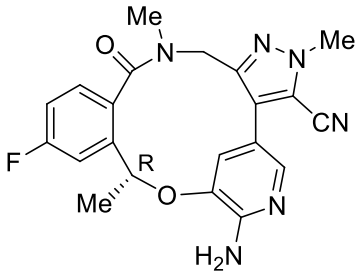
Drug Substance

Non-proprietary name of the drug substance(s): Lorlatinib

Chemical name: (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile

Molecular formula and molecular mass: C21H19FN6O2; 406.41 daltons

Structural formula:



Physicochemical properties: Lorlatinib is a white to off-white powder with a pKa of 4.92. The solubility of lorlatinib in aqueous media decreases over the range pH 2.55 to pH 8.02 from 32.38 mg/mL to 0.17 mg/mL. The log of the distribution coefficient (octanol/water) at pH 9 is 2.45.

14. Clinical Trials

14.1. Clinical Trials by Indication

Previously Untreated ALK-Positive Metastatic Non-Small Cell Lung Cancer (Phase 3 Study B7461006, CROWN study)

Table 7. Summary of Patient Demographics for Clinical Trials in ALK-positive Patients Treated with LORBRENA and Crizotinib in Phase 3 Study B7461006

Characteristic	LORBRENA n=149	Crizotinib n=147	Total N=296
Age (years), n (%)			
Median (range)	61 (30-90)	56 (26-84)	59 (26-90)
≥65	59 (40)	44 (30)	103 (35)
<65	90 (60)	103 (70)	193 (65)
Sex, n (%)			
Male	65 (44)	56 (38)	121 (41)

Characteristic	LORBRENA n=149	Crizotinib n=147	Total N=296
Female	84 (56)	91 (62)	175 (59)
Race, n (%)			
White	72 (48)	72 (49)	144 (49)
Asian	65 (44)	65 (44)	130 (44)
Black or African American	0	1 (0.7)	1 (0.3)
ECOG performance status, n (%)			
0	67 (45)	57 (39)	124 (42)
1	79 (53)	81 (55)	160 (54)
2	3 (2)	9 (6)	12 (4)
Smoking Status, n (%)			
Never smoked	81 (54)	94 (64)	175 (59)
Previous Smoker	55 (37)	43 (29)	98 (33)
Current Smoker	13 (9)	9 (6)	22 (7)
Current Stage of Disease, n (%)			
IIIA	1 (0.7)	0	1 (0.3)
IIIB	12 (8)	8 (5)	20 (7)
IV	135 (91)	139 (95)	274 (93)
Other	1 (0.7)	0	1 (0.3)
Histologic Type, n (%)			
Adenocarcinoma	140 (94)	140 (95)	280 (95)
Adenosquamous carcinoma	6 (4)	5 (3)	11 (4)
Large cell carcinoma	0	1 (0.7)	1 (0.3)
Squamous cell carcinoma	3 (2)	1 (0.7)	4 (1)
Patients with prior anti-cancer systemic therapy, n (%)*			
Yes	12 (8)	9 (6)	21 (7)
No	137 (92)	138 (94)	275 (93)
Patients with prior brain radiotherapy, n (%)			
Yes	9 (6)	10 (7)	19 (6)

Characteristic	LORBRENA n=149	Crizotinib n=147	Total N=296
CNS Metastases at Baseline, n (%)			
Present	38 (26)	40 (27)	78 (26)

* According to the protocol, previous adjuvant or neoadjuvant anticancer therapy was allowed if it had been completed more than 12 months before randomization.

The efficacy of LORBRENA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (CROWN study). Patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. Neurologically stable patients with treated or untreated asymptomatic CNS metastases, including leptomeningeal metastases, were eligible. Patients were required to have finished radiation therapy, including stereotactic or partial brain irradiation within 2 weeks prior to randomization; whole brain irradiation within 4 weeks prior to randomization. Patients with severe acute or chronic psychiatric conditions, including recent (within the past year) or active suicidal ideation or behavior, were excluded.

Patients were randomized 1:1 to receive LORBRENA 100 mg orally once daily or crizotinib 250 mg orally twice daily. Randomization was stratified by ethnic origin (Asian vs. non-Asian) and the presence or absence of CNS metastases at baseline. Treatment on both arms was continued until disease progression or unacceptable toxicity.

A total of 296 patients were randomized to LORBRENA (n=149) or crizotinib (n=147). The demographic characteristics of the overall study population were: median age 59 years (range: 26 to 90 years), age ≥65 years (35%), 59% female, 49% White, 44% Asian, and 0.3% Black. The majority of patients had adenocarcinoma (95%) and never smoked (59%). CNS metastases as determined by Blinded Independent Central Review (BICR) neuroradiologists were present in 26% (n=78) of patients: of these, 30 patients had measurable CNS lesions.

The primary efficacy outcome measure was progression-free survival (PFS) as determined by BICR according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1). Additional secondary efficacy outcome measures included overall survival (OS), overall response rate (ORR), duration of response (DOR), time to intracranial progression (IC-TTP) evaluated by BICR. In patients with measurable CNS metastases at baseline, additional outcome measures were intracranial overall response rate (IC-ORR) and intracranial duration of response (IC-DOR) all by BICR.

Efficacy results from Study B7461006 (CROWN study) as assessed by BICR are summarized in Table 8 and Figure 1. Results from study demonstrated a significant improvement in PFS for the LORBRENA arm over the crizotinib arm. The median (95% CI) PFS follow-up duration was 18.3 months (16.4, 20.1) and 14.8 months (12.8, 18.4) for participants assigned to the LORBRENA arm and to the crizotinib arm, respectively. The benefit from lorlatinib treatment was comparable across subgroups of baseline patient and disease characteristics. At the data cutoff point OS data was not mature. In the analysis of IC-TTP, the percentage of patients without CNS progression at 12 months was 96% for the LOBRENA arm at 60% for crizotinib.

Table 8. Efficacy Results in Study B7461006

Efficacy Parameter	LORBRENA n=149	Crizotinib n=147
Progression-free survival		
Number of events, n (%)	41 (28%)	86 (59%)
Progressive disease, n (%)	32 (22%)	82 (56%)
Death, n (%)	9 (6%)	4 (3%)
Median, months (95% CI)[a]	NE (NE, NE)	9.3 (7.6, 11.1)
Hazard ratio (95% CI)[b]	0.28 (0.19, 0.41)	
p-value*	<0.0001	
Overall response rate		
Overall response rate (95% CI)[c]	76% (68, 83)	58% (49, 66)
Complete response	3%	0%
Partial response	73%	58%
Duration of response		
Number of responders, n	113	85
Median, months (95% CI)[a]	NE (NE, NE)	11.0 (9.0, 12.9)
Response duration ≥6 months, n (%)	101 (89%)	53 (62%)
Response duration ≥12 months, n (%)	79 (70%)	23 (27)%
Response duration ≥18 months, n (%)	34 (30%)	9 (11%)

Abbreviations: CI=confidence interval; N=number of patients; NE=not estimable; PFS=progression free survival.

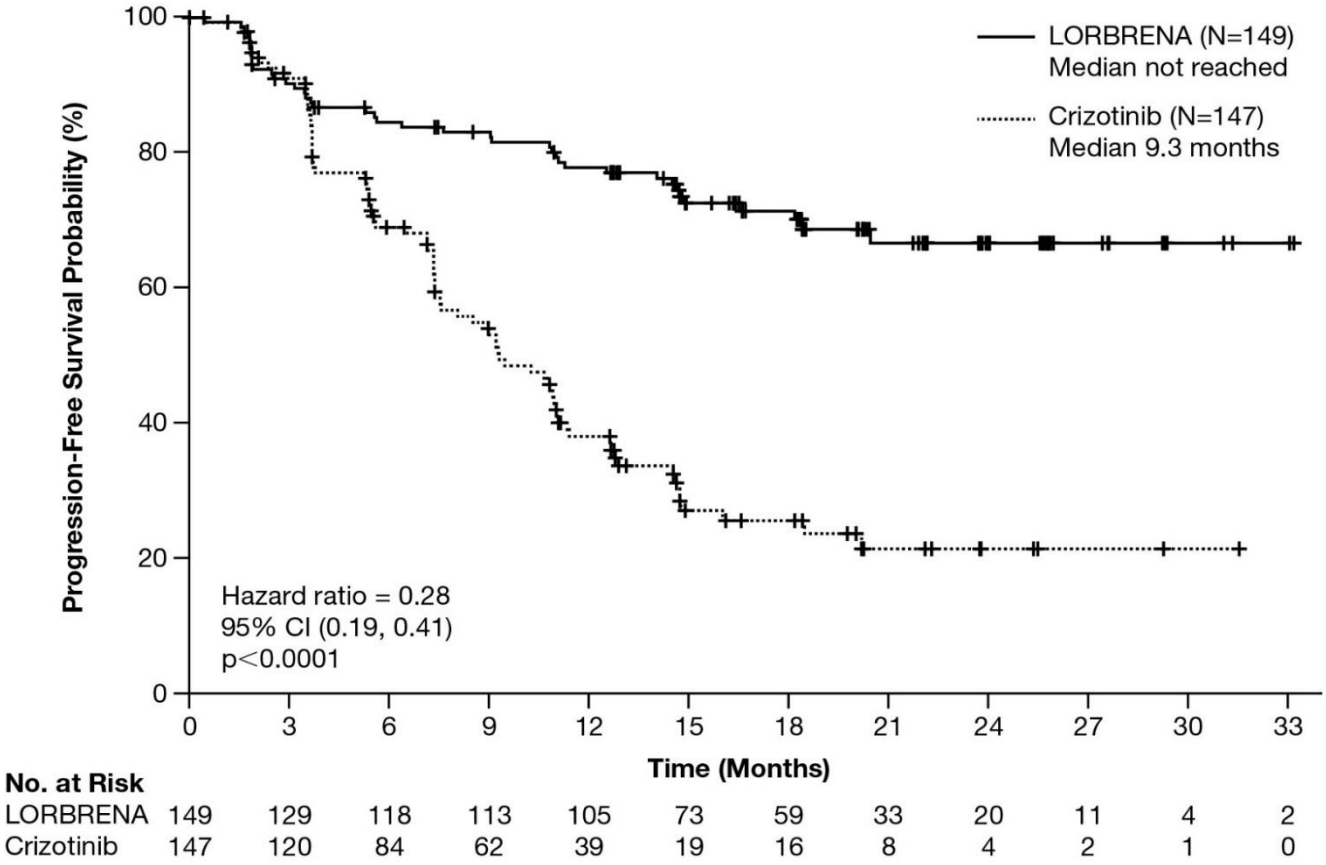
* p-value based on 1-sided stratified log-rank test.

[a] Based on the Brookmeyer and Crowley method.

[b] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio <1 indicates a reduction in hazard rate in favor of lorlatinib.

[c] Using exact method based on binomial distribution.

Figure 1: Kaplan-Meier Plot of Progression-Free Survival by BICR in Phase 3 Study B7461006



The results of prespecified, exploratory secondary analyses of intracranial response rate in 30 patients with measurable CNS lesions at baseline as assessed by BICR are summarized in Table 9.

Table 9. Intracranial Responses in Patients with Measurable Intracranial Lesions at Baseline in Study B7461006

Intracranial Tumor Response Assessment	LORBRENA N=17	Crizotinib N=13
Intracranial response rate (95% CI)[a]	82% (57, 96)	23% (5, 54)
Complete response	71%	8%
Duration of response		
Number of responders, n	14	3
Response duration ≥12 months, n (%)	11 (79%)	0

Abbreviations: CI=confidence interval; N/n=number of patients.

[a] Using exact method based on binomial distribution.

Previously Treated ALK-Positive Metastatic NSCLC (Phase 1/2 Study B7461001)

Table 10. Summary of Patient Demographics for Clinical Trials in Previously Treated ALK-Positive Metastatic NSCLC

Study #	Study design	Dosage, route of administration and duration
B7461001	Single arm, multicenter Phase 1/2 study	LORBRENA orally at the recommended dose of 100 mg once daily, continuously

The use of LORBRENA in the treatment of ALK positive advanced NSCLC previously treated with 1 or more ALK TKIs was investigated in B7461001, a single arm, multicenter Phase 1/2 study. A total of 197 patients with ALK positive metastatic NSCLC previously treated with 1 or more ALK TKIs were enrolled in the Phase 2 portion of the study. Patients received LORBRENA orally at the recommended dose of 100 mg once daily, continuously.

Patients were required to have metastatic disease with at least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1), ECOG performance status of 0 to 2, and documented ALK rearrangement in tumor tissue as determined by fluorescence in situ hybridization (FISH) assay or by Immunohistochemistry (IHC). Patients with asymptomatic CNS metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were eligible. Patients with severe, acute, or chronic psychiatric conditions including suicidal ideation or behavior were excluded.

Table 11 presents an overview of the patients in the different cohorts, pooled cohorts, and their respective sizes in the Phase 2 study portion.

Table 11. Efficacy Cohorts of ALK-Positive NSCLC Patients Assessed by ICR (Phase 2)

Study Portion	Cohort Name	Cohort Description	Total Number of Patients n	Patients with Brain Metastases at Baseline n
Phase 2	EXP-2:5	1 or more prior ALK TKI ± chemotherapy	197	132
	EXP-4:5	2 or more prior ALK TKI ± chemotherapy	111	83
	EXP-2:3A	Prior crizotinib only ± prior chemotherapy	59	37

Study Portion	Cohort Name	Cohort Description	Total Number of Patients n	Patients with Brain Metastases at Baseline n
	EXP-3B	1 prior non-crizotinib ALK TKI ± chemotherapy	27	12

Abbreviations: ALK=anaplastic lymphoma kinase; EXP=expansion; ICR=independent central review; N/n=number of patients; N/A=not applicable; NSCLC=non-small-cell lung cancer; TKI=tyrosine kinase inhibitor.

Patient demographics of the 197 ALK positive advanced NSCLC patients previously treated with 1 or more ALK TKIs, were 117 (59%) female, 97 (49%) Caucasian, 70 (36%) Asian and the mean age was 53 years (range: 29 to 85 years) with 19% ≥ 65 years of age. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 or 1 in 190 (97%) patients and 2 in 7 (4%) patients. Brain metastases were present at baseline in 123 (62%) patients. All 197 patients had received prior systemic therapy: 39 (20%) received 1, 55 (28%) received 2, 38 (19%) received 3 and 66 (34%) received 4 or more prior systemic therapies, respectively. Of the 197 patients: 87 (44%) received 1 prior ALK TKI, 65 (33%) received 2 prior ALK TKIs, and 46 (23%) received 3 or more prior ALK TKIs.

The primary efficacy endpoint in the Phase 2 portion of the study was objective response rate (ORR), including intracranial ORR, as per Independent Central Review (ICR) according to modified Response Evaluation Criteria in Solid Tumors (modified RECIST version 1.1). Secondary endpoints included duration of response (DOR), intracranial DOR, time to tumor response (TTR), and progression free survival (PFS).

The main efficacy results for study B7461001 are included in Tables Table 12 and Table 13.

Table 12. Efficacy Results in B7461001

Efficacy Parameter	Pooled EXP-2:5 1 or more ALK TKIs (N = 197)
Objective response rate[a] (95% CI)[b]	47.2% [40.1, 54.4]
Complete response, n	4
Partial response, n	89
Duration of response	
Median, months	NR
(95% CI)[c]	(11.1, NR)
Progression-free survival	
Median, months	7.4
(95% CI)[c]	(5.6, 11.0)

Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; EXP=expansion; ICR=Independent Central Review; N/n=number of patients; NR=not reached; TKI=tyrosine kinase inhibitor.

[a] Per ICR.

[b] Using exact method based on binomial distribution.

[c] Using the Brookmeyer Crowley method.

Table 13. Intracranial Efficacy Results in B7461001*

Efficacy Parameter	Pooled EXP-2:5 1 or more ALK TKIs (N = 132)
Objective response rate[a] (95% CI)[b]	53.0% (44.2, 61.8)
Complete response, n	35
Partial response, n	35
Duration of response Median, Months (95% CI)[c]	14.5 (NR, NR)

*In patients with at least 1 measurable baseline brain metastasis
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; DOR=duration of response; EXP=expansion; ICR=Independent Central Review; N/n=number of patients; NSCLC=non-small cell lung cancer; NR=not reached; ORR=objective response rate; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.
[a] Per ICR.
[b] Using exact method based on binomial distribution.
[c] Using the Brookmeyer Crowley method.

Among the 93 patients with a confirmed objective response by ICR, the median time to response (TTR) was 1.4 months (range: 1.1 to 11.0 months). Among the 70 patients with a confirmed objective tumour response by ICR, the median intracranial TTR was 1.4 months (range: 1.1 to 6.2 months).

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General Toxicology

The main toxicities observed were inflammation across multiple tissues (with increases in white blood cells), and changes in the pancreas (with increases in amylase and lipase), hepatobiliary system (with increases in liver enzymes), male reproductive system, cardiovascular system, kidneys and gastrointestinal tract, peripheral nerves and the central nervous system (potential for cognitive functional impairment) (approximately 4.6 to 21 times the human clinical exposure at 100 mg based on AUC for all toxicities). Changes in blood pressure and heart rate, and QRS and PR interval prolongation

were also observed in animals after acute dosing (approximately 2.6 times the human clinical exposure at 100 mg after a single dose based on C_{max}). All target organ findings with the exception of the hepatic bile duct hyperplasia (approximately 7.1 to 21 times the human clinical exposure at 100 mg based on AUC) were partially to fully reversible.

Carcinogenicity

Carcinogenicity studies have not been conducted with lorlatinib.

Genotoxicity

Lorlatinib was not mutagenic in a bacterial reverse mutation (Ames) assay. Lorlatinib induced micronuclei via an aneugenic mechanism in human lymphoblastoid TK6 cells in vitro and in the bone marrow of rats. The exposure of animals at the no observed effect level for aneugenicity was approximately 16.5 times human clinical exposure at 100 mg based on AUC.

Reproductive and developmental toxicology

Effects on male reproductive organs (testis, epididymis, and prostate) were observed in animals (approximately 3.9 to 1.6 times the human clinical exposure at 100 mg based on AUC). The effects on male reproductive organs were fully or partially reversible.

In embryo-fetal toxicity studies increased embryolethality, and lower fetal body weights were observed. Fetal morphologic abnormalities included rotated limbs, supernumerary digits, gastroschisis, malformed kidneys, domed head, high arched palate, and dilation of ventricles of the brain. The lowest doses with embryo-fetal effects in animals correlated with 0.6 to 1.1 times the human clinical exposure at 100 mg, based on AUC.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]LORBRENA®

Lorlatinib tablets

This Patient Medication Information is written for the person who will be taking **LORBRENA.** This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **LORBRENA**, talk to a healthcare professional.

Serious warnings and precautions box

LORBRENA should only be prescribed by a healthcare professional experienced in the use of anti-cancer drugs.

LORBRENA can cause serious side effects which may include:

- **High blood lipid levels (cholesterols or triglycerides):** LORBRENA can cause your blood lipid levels to increase. Your healthcare professional will do regular blood tests while you are taking LORBRENA to check your blood lipid levels.
- **Lung problems:** LORBRENA can cause severe or life-threatening swelling (inflammation) of the lungs that can lead to death. Symptoms may be similar to those from lung cancer. Tell your healthcare professional immediately if you have any new or worsening symptoms of lung problems, including trouble breathing, shortness of breath, cough, or fever.
- **Liver problems:** LORBRENA can cause serious liver problems if it is taken with other medicines. Tell your healthcare professional about all the other medicines you take. While you are taking LORBRENA, if you experience yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting and/or loss of appetite, contact your healthcare professional immediately.

What LORBRENA is used for:

LORBRENA is used to treat adults with a type of lung cancer called non-small cell lung cancer (NSCLC). It is used in a special type of NSCLC that is anaplastic lymphoma kinase (ALK)-positive. The ALK-positive NSCLC has spread to other parts of the body and:

- has gotten worse after taking crizotinib and at least one other ALK tyrosine kinase inhibitor (TKI) drug, or
- has gotten worse after taking ceritinib or alectinib.

LORBRENA is used to treat adult patients with a type of lung cancer called non-small cell lung cancer (NSCLC). It is used in a special type of NSCLC that is anaplastic lymphoma kinase (ALK) positive. The ALK-positive NSLC:

- has grown outside of the lung or has spread to other parts of the body; and
- cannot be cured with surgery or other treatment (like chemotherapy or radiation); and
- has not been treated before.

LORBRENA is not approved for use in children.

How LORBRENA works:

LORBRENA belongs to a group of anti-cancer medicines called ALK tyrosine kinase inhibitors (TKI). It blocks the action of an enzyme called 'ALK tyrosine kinase'. By blocking this enzyme LORBRENA may slow down or stop the growth of your cancer. It may also help to shrink your cancer.

If you have any questions about how LORBRENA works or why this medicine has been prescribed for you, ask your healthcare professional.

The ingredients in LORBRENA are:

Medicinal ingredient: lorlatinib

Non-medicinal ingredients: dibasic calcium phosphate anhydrous, ferrosofferic oxide/black iron oxide, hydroxypropyl methylcellulose/hypromellose, iron oxide red, lactose monohydrate, macrogol/polyethylene glycol, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, triacetin

LORBRENA comes in the following dosage form:

Tablets, 25 mg, 100 mg

Do not use LORBRENA if:

- you are allergic to lorlatinib or any of the other ingredients of LORBRENA;
- you are taking any of these medicines:
  - rifampicin (used to treat tuberculosis);
  - carbamazepine, phenytoin (used to treat epilepsy);
  - enzalutamide (used to treat prostate cancer);
  - mitotane (used to treat cancer of the adrenal glands);
  - medicines containing St. John's wort (Hypericum perforatum, a herbal preparation).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LORBRENA. Talk about any health conditions or problems you may have, including if you:

- have high blood lipid levels (cholesterol or triglycerides);
- have heart problems;
- have lung problems;
- have kidney problems;
- have liver problems;
- have pancreas problems;
- have high blood pressure;
- have high blood sugar;

- have any other medical conditions;
- are intolerant to lactose;
- are pregnant, or plan to become pregnant. You should not get pregnant or father a child while you are taking LORBRENA. LORBRENA can harm your unborn baby.
  - **Females** who are able to become pregnant must use effective, non-hormonal birth control during treatment with LORBRENA and for at least 21 days after the final dose of LORBRENA. If hormonal birth control use cannot be avoided, use condoms in addition to hormonal birth control for at least 21 days after the final dose of LORBRENA.
  - **Males** who have pregnant partners or female partners who can become pregnant must use condoms during treatment with LORBRENA and for at least 97 days after the final dose of LORBRENA.
  - Talk to your healthcare professional about birth control methods that may be right for you.
  - If you or your partner becomes pregnant, tell your healthcare professional right away.
  - LORBRENA can cause decreased fertility in both males and females. If you may want to become pregnant or father a child after treatment with LORBRENA talk to your healthcare professional about fertility preservation options that may be right for you.
- are breastfeeding or plan to breastfeed. It is not known if LORBRENA passes into your breast milk. Do not breastfeed during treatment with LORBRENA and for 7 days after the final dose. Talk to your healthcare professional about the best way to feed your baby during this time.

Other warnings you should know about:

- Your healthcare professional will test your cancer before you start taking LORBRENA to make sure it is ALK-positive.
- **High blood lipids levels (hypercholesterolemia or hypertriglyceridemia):**
  - Your healthcare professional will do a blood test to check your blood lipid levels before you start taking LORBRENA. Once you start taking LORBRENA your healthcare professional will do blood tests after 2 weeks, 4 weeks, and 8 weeks. Your healthcare professional may also do blood tests at other times during your treatment.
  - If your blood lipid levels increase while you are taking LORBRENA, your healthcare professional may need to start you on a lipid-lowering medicine to lower the levels.
  - If you are already taking a lipid-lowering medicine, your healthcare professional may need to increase your dose of that medicine.
- **Serious lung problems:** LORBRENA can cause **interstitial lung disease and pneumonitis** (severe or life-threatening swelling /inflammation of the lungs) that can lead to death. Symptoms may be similar to those from lung cancer. Tell your healthcare professional immediately if you have any new or worsening symptoms of lung problems, including trouble breathing, shortness of breath, cough, or fever.
- **Serious liver problems:** LORBRENA can cause serious liver problems if it is taken with other medicines. Tell your healthcare professional about all the other medicines you take. While you are taking LORBRENA, if you experience yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting and/or loss of appetite, contact your healthcare professional immediately.
- **Mental status changes, speech problems, mental health problems, and seizures:**
  - LORBRENA can cause problems with thinking (such as forgetfulness or confusion), trouble with speech, changes in sleep or mood, psychotic effects/hallucinations (seeing

or hearing things that are not real) and seizures. Tell your healthcare professional right away if you have these symptoms.
    - Your healthcare professional may change your dose of LORBRENA if these symptoms occur. If these symptoms are severe, your healthcare professional may tell you to stop taking LORBRENA.
- **Heart Rhythm problems: LORBRENA may cause very slow or abnormal heartbeats.** Your healthcare professional may need to check your heart closely while you are taking LORBRENA. Tell your healthcare professional right away if you feel dizzy or faint or have abnormal heartbeats. If you have these symptoms, your healthcare professional may need to change your dose of LORBRENA.
- **Hypertension (increases in blood pressure):**
    - LORBRENA may cause high blood pressure. Your healthcare professional should check your blood pressure before starting LORBRENA. Once you start taking LORBRENA they will do blood pressure tests after 2 weeks and monthly thereafter during your treatment.
    - Tell your healthcare provider if you have headaches, dizziness, blurred vision, chest pain, shortness of breath, or swelling. They might give you medicine to treat your high blood pressure.
- **Hyperglycemia (increases in blood sugar):**
    - LORBRENA may increase your blood sugar levels. Your healthcare professional should do blood tests to check your blood sugar levels before starting and during treatment with LORBRENA.
    - Tell your healthcare professional if you are feeling very thirsty, very hungry, weak or tired, confused, have dry skin, a headache or blurry vision, or need to urinate more often.
    - Your healthcare professional may need to give or change your blood sugar medicine. This will help control your blood sugar levels.

Driving and using machines

LORBRENA can affect your ability to drive and use machines. Avoid driving or using machinery until you know how LORBRENA affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LORBRENA:

- boceprevir, telaprevir, medicines used to treat hepatitis C;
- conivaptan, a medicine used to increase sodium levels in hospitalized patients;
- efavirenz, cobicistat, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either danoprevir, elvitegravir, indinavir, lopinavir, saquinavir or tipranavir, medicines used to treat AIDS/HIV;
- fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole, medicines used to treat fungal infections. Also troleandomycin, a medicine used to treat certain types of bacterial infections;
- quinidine, a medicine used to treat irregular heartbeat and other heart problems;
- pimozide, a medicine used to treat mental health problems;
- alfentanil and fentanyl, medicines used to treat severe pain;
- hormonal contraceptives;

- ciclosporin, sirolimus, and tacrolimus, medicines used in organ transplantation to prevent transplant organ rejection;
- rifampicin, a medicine used to treat tuberculosis;
- carbamazepine, phenytoin, medicines used to treat epilepsy;
- enzalutamide, a medicine used to treat prostate cancer;
- mitotane, a medicine used to treat cancer of the adrenal glands;
- medicines containing St. John's wort (Hypericum perforatum, a herbal preparation);
- grapefruit juice or any products containing grapefruit juice.

How to take LORBRENA:

- Take LORBRENA exactly as your healthcare professional tells you.
- Do not change your dose or stop taking LORBRENA unless your healthcare professional tells you to.
- Swallow LORBRENA tablets whole. Do not chew, crush or split LORBRENA tablets before swallowing them.
- You may take LORBRENA with or without food.
- You should not eat or drink grapefruit products during your treatment with LORBRENA. It may increase the amount of LORBRENA in your blood to a harmful level.
- If you vomit after taking a dose of LORBRENA, do not take an extra dose; just take your next dose at your regular time.

Usual dose:

The recommended dose is 100 mg taken orally once daily. Your healthcare professional may adjust your dose if you have severe kidney or moderate to severe liver problems.

If you have side effects, your healthcare professional may need to change your dose, temporarily stop, or completely stop your treatment with LORBRENA.

Overdose:

If you think you, or a person you are caring for, have taken too much LORBRENA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a dose, take it as soon as you remember. If it is close to your next dose (within 4 hours), just take your next dose at your regular time. Do not take two doses at the same time to make up for a missed dose.

Possible side effects from using LORBRENA:

These are not all the possible side effects you may have when taking LORBRENA. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of LORBRENA include:

- feeling of numbness or pins and needles in the joints, arms or legs (peripheral neuropathy);

- tiredness (fatigue);
- weight gain;
- pain in your joints;
- muscle pain, back pain, pain in your arms or legs;
- diarrhea;
- nausea, vomiting;
- headache;
- dizziness;
- rash;
- cough;

Your healthcare professional will conduct tests before you start taking LORBRENA and regularly during your treatment. These tests will include measurements of your blood pressure and heart rate as well as blood tests. LORBRENA can cause abnormal blood test results, including high blood fat levels. Your healthcare professional will decide when to perform blood tests and will interpret the results. These results will tell your healthcare professional how LORBRENA is affecting your muscles, liver and pancreas.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Anemia (decreased number of red blood cells): fatigue/weakness, loss of energy, irregular heartbeats, pale complexion, shortness of breath		X	
Changes in mental status, speech problems, and seizures: confusion, memory loss, trouble with attention, difficulty speaking, such as slurred or slow speech, muscle jerk and spasms throughout the body, with or without loss of consciousness		X	
Edema: swelling of the legs, ankles, feet and hands		X	
Hypertension (high blood pressure): shortness of breath, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs		X	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Increased blood levels of amylase or lipase: weight loss or nausea, or abdominal pain that gets worse with eating and may spread to the back		X	
Increased blood level of creatine phosphokinase: unexplained muscle pain, tenderness or weakness		X	
Increased levels of liver enzymes (ALT, AST) in the blood; **Liver problems:** if it is taken with other medicines**:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, fatigue		X	
Lymphopenia (decrease in number of lymphocytes, a type of white blood cell): infections		X	
Mental health problems: changes in mood or sleep, irritability, agitation, mood swings, anxiety, depression, psychotic effects/hallucinations (seeing or hearing things that aren't real)		X	
Vision problems: double vision, sensitivity to light, blurred vision, vision loss, floaters, flashes of light		X	
Common			
Heart rhythm problems: feel dizzy or faint or have very slow or abnormal heartbeats		X	
Hyperglycemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		X	
Serious lung problems (such as interstitial lung disease, pneumonitis, pneumonia): new or worsening difficulty breathing,			X

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
chest pain, shortness of breath, cough with or without mucous, or fever			
Respiratory failure (lung failure): blue color on skin, lips, and fingernails; feel sleepy; irregular heartbeats; loss of consciousness; sudden worsening of shortness of breath			X
Upper respiratory tract infection, bronchitis (a cold, inflamed bronchial tubes): fatigue, runny or stuffy nose, sore throat, cough with or without phlegm, sinus congestion, body aches, headache, sneezing, fever, generally feeling unwell		X	
Uncommon			
Myocardial infarction, heart failure (heart attack, heart doesn't pump as well as it should): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue/weakness, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint, irregular heartbeat, swelling in ankles, legs and feet, lack of appetite, nausea			X
Peripheral Artery Occlusion (blocked artery in arm or leg): leg pain when walking, weakness, or cramping in muscles			X
Pulmonary edema (excess fluid in the lungs): difficulty breathing that worsens with activity or when lying down, extreme shortness of breath, wheezing or gasping for			X

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
breath, cold clammy skin, irregular heartbeat, cough that produces frothy sputum, blue-tinged lips			
Pulmonary embolism (blood clot in the lung): chest pain that may increase with deep breathing, cough, coughing up bloody sputum, shortness of breath			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15°C to 30°C in the original package to protect from light.

Keep out of reach and sight of children.

If you want more information about LORBRENA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (canada.ca/en/health-canada/services/drugs-health-products/drugs-products/drug-product-database.html); the manufacturer's website http://www.Pfizer.ca, or by calling 1-800-463-6001.

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