

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **LORBRENA™**

Lorlatinib tablets

tablets, 25 and 100 mg, oral

Tyrosine Kinase Inhibitor

“ LORBRENA (lorlatinib) is indicated as 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. *Patients should be advised of the nature of the authorization. For further information for LORBRENA please refer to Health Canada’s [Notice of Compliance with conditions - drug products](#) web site.*”

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™Pfizer Inc,  
Pfizer Canada ULC, Licensee

**This product has been authorized under the  
Notice of Compliance with Conditions (NOC/c)  
for one or all of its indicated uses.**

### **What is a Notice of Compliance with Conditions (NOC/c)?**

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

### **What will be different about this Product Monograph?**

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

### **Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph**

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

## RECENT MAJOR LABEL CHANGES

CONTRAINDICATIONS (2)	01-2020
WARNINGS AND PRECAUTIONS (6)	01-2020

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“LORBRENA (lorlatinib) is indicated as 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. *Patients should be advised of the nature of the authorization. For further information for LORBRENA please refer to Health Canada’s Notice of Compliance with conditions - drug products web site:* <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>”

## PART I: HEALTH PROFESSIONAL INFORMATION

### NOC/c 1 INDICATIONS

LORBRENA (lorlatinib) is indicated as 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 with conditions was based on a primary efficacy endpoint of tumor objective response rate and duration of response; no overall survival benefit has been demonstrated (see **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 275 ALK-positive NSCLC patients treated with LORBRENA, 53 (19.3%) were ≥65 years of age. The limited data on the safety and efficacy of lorlatinib in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

### NOC/c 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 **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 **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

## NOC/c 3 DOSAGE AND ADMINISTRATION

### 3.1 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 **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 **DRUG INTERACTIONS** and **ACTION AND 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.

#### **Hepatic impairment:**

A formal hepatic impairment study has not been conducted with lorlatinib. No dose adjustments are recommended for patients with mild hepatic impairment. Limited information is available for LORBRENA in patients with moderate or severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**).

#### **Renal impairment:**

A formal renal impairment study has not been conducted with lorlatinib. No dose adjustment is needed for patients with mild (creatinine clearance [ $CL_{cr}$ ]: 60-89 mL/min) or moderate ( $CL_{cr}$ : 30-59 mL/min) renal impairment based on a population pharmacokinetic analysis. Information for LORBRENA use in patients with severe ( $CL_{cr}$ : <30 mL/min) renal impairment is limited (n=1). (see **ACTION AND CLINICAL PHARMACOLOGY**).

### 3.2 Recommended Dose and Dosage Adjustment

#### **Recommended Dose**

The recommended dose of LORBRENA is 100 mg taken orally once daily continuously. Continue treatment with LORBRENA as long as the patient is deriving clinical benefit from therapy.

LORBRENA may be taken with or without food (see **ACTION AND CLINICAL PHARMACOLOGY**).

#### **Pediatric patients:**

The safety and efficacy of LORBRENA in pediatric patients have not been established.

#### **Elderly ( $\geq 65$ years):**

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.

## 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
<b>Hypercholesterolemia or Hypertriglyceridemia</b>	
Mild hypercholesterolemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L)  <u>OR</u>  Mild hypertriglyceridemia (triglycerides between 150 and 300 mg/dL or 1.71 and 3.42 mmol/L)	Introduce or modify lipid-lowering therapy <sup>a</sup> 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)  <u>OR</u>  Moderate hypertriglyceridemia (triglycerides between 301 and 500 mg/dL or 3.43 and 5.7 mmol/L)	
Severe hypercholesterolemia (cholesterol between 401 and 500 mg/dL or between 10.35 and 12.92 mmol/L)  <u>OR</u>  Severe hypertriglyceridemia (triglycerides between 501 and 1000 mg/dL or 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy; <sup>a</sup> if currently on lipid-lowering therapy, increase the dose of this therapy <sup>a</sup> in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue LORBRENA at the same dose without interruption.

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

<b>Adverse Reaction</b>	<b>LORBRENA Dosing</b>
Grade 4 hypercholesterolemia (cholesterol over 500 mg/dL or over 12.92 mmol/L)	Introduce the use of lipid-lowering therapy <sup>a</sup> or increase the dose of this therapy <sup>a</sup> 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.
<u>OR</u>	Re-challenge at same LORBRENA dose while maximizing lipid-lowering therapy <sup>a</sup> in accordance with respective prescribing information.
Grade 4 hypertriglyceridemia (triglycerides over 1000 mg/dL or over 11.4 mmol/L)	If severe hypercholesterolemia and/or hypertriglyceridemia recurs despite maximal lipid-lowering therapy <sup>a</sup> in accordance with respective prescribing information, reduce LORBRENA by 1 dose level.
<b>Central nervous system effects<sup>b,c</sup></b>	
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	Withhold dose until toxicity is less than or equal to Grade 1. Then resume LORBRENA at 1 reduced dose level.
<u>OR</u>	
Grade 3: Severe	Permanently discontinue LORBRENA.
Grade 4: Life-threatening/Urgent intervention indicated	
<b>Interstitial Lung Disease (ILD)/Pneumonitis</b>	
Any Grade treatment-related ILD/Pneumonitis	Permanently discontinue LORBRENA.
<b>Other adverse reactions<sup>c</sup></b>	
Grade 1	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
<u>OR</u>	
Grade 2	Withhold LORBRENA until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume LORBRENA at 1 reduced dose level.
Greater than or equal to Grade 3	

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

<sup>a</sup> Lipid-lowering therapy may include: HMG CoA reductase inhibitor, nicotinic acid, fibric acid, or



ethyl esters of omega-3 fatty acids.

- <sup>b</sup> Examples of CNS effects comprise hallucination and changes in cognition, mood, mental status or speech (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).
- <sup>c</sup> 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 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.

### 3.3 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.

### 3.4 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.

## 4 OVERDOSAGE

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 management of a suspected drug overdose, contact your regional poison control centre.

## 5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table – Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated tablet 25 mg, 100 mg	<u>Tablet core contains:</u> dibasic calcium phosphate anhydrous, magnesium stearate, microcrystalline cellulose, sodium starch glycolate  <u>Film-coating contains:</u> ferrousferic oxide/Black iron oxide, hydroxypropyl methylcellulose (HPMC) 2910/hypromellose, iron oxide red, lactose monohydrate, macrogol/polyethylene glycol (PEG) 3350, titanium dioxide, triacetin

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 (lorlatinib) 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)

NOC/c

## 6 WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

- Hypercholesterolemia/Hypertriglyceridemia (see **WARNINGS AND PRECAUTIONS, Hyperlipidemia**)
- Pneumonitis (see **WARNINGS AND PRECAUTIONS, Respiratory**)
- Hepatotoxicity (see **WARNINGS AND PRECAUTIONS, 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.

### 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.

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.

Avoid concomitant use of LORBRENA with moderate CYP3A inducers (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

### Cardiovascular

#### ***Atrioventricular (AV) Block***

PR interval prolongation and atrioventricular (AV) block events have been reported in patients receiving LORBRENA. In 295 patients who received LORBRENA at a dose of 100 mg orally once daily in Study B7461001 and who had a baseline electrocardiography (ECG), 3 patients

(1%) experienced AV block and 1 patient (0.3%) experienced Grade 3 AV block and underwent pacemaker placement.

For those patients who develop AV block, dose modification may be required (see **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 **ADVERSE REACTIONS**, Nervous System Disorders).

### **Endocrine and Metabolism**

#### ***Hyperlipidemia***

The use of LORBRENA has been associated with increases in serum cholesterol and triglycerides (see **ADVERSE REACTIONS**). Grade 3 or 4 elevations in total cholesterol occurred in 54 patients (17%) and Grade 3 or 4 elevations in triglycerides occurred in 55 patients (17%) of the 332 patients who received LORBRENA in Study B7461001. No patient was permanently discontinued from treatment with lorlatinib associated with hypercholesterolemia or hypertriglyceridemia.

Initiation, or increase in the dose, of lipid-lowering agents is recommended (see **DOSAGE AND ADMINISTRATION**).

### **Neurologic**

#### ***Central Nervous System Effects***

Central nervous system (CNS) effects have been observed in patients receiving LORBRENA (see **ADVERSE REACTIONS**). Cognitive effects occurred in 95 (29%) of the 332 patients who received LORBRENA at any dose in Study B7461001; in 7 patients (2.1%) these events were severe (Grade 3 or 4). Mood effects occurred in 76 patients (23%); in 6 patients (1.8%) these events were severe. Speech effects occurred in 38 patients (11%); in 1 patient (0.3%) the event was severe. Hallucinations occurred in 23 patients (7%); in 2 patients (0.6%) these events were severe. Mental status changes occurred in 7 patients (2.1%); in 6 patients (1.8%) these events were severe. 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 **DOSAGE AND ADMINISTRATION**).

### **Respiratory**

#### ***ILD/Pneumonitis***

Severe or life-threatening pulmonary adverse reactions consistent with pneumonitis have occurred with LORBRENA. Pneumonitis occurred in 4 patients (1.2%) who received LORBRENA at any dose in Study B7461001, including Grade 3 or 4 pneumonitis in 3 patients (0.9%). 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 **DOSAGE AND ADMINISTRATION**).

### **Sexual Health**

#### ***Reproduction***

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 **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 **NON-CLINICAL TOXICOLOGY**). It is not known whether LORBRENA affects female fertility. Men should seek advice on effective fertility preservation before treatment.

## **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***

Avoid concomitant use of LORBRENA with moderate CYP3A inducers. If concomitant use of moderate CYP3A inducers cannot be avoided, monitor AST, ALT, and bilirubin 48 hours after initiating LORBRENA and at least 3 times during the first week after initiating LORBRENA (see **WARNINGS AND PRECAUTIONS, Drug-Drug Interactions, Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers; DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS**).

### ***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 **WARNINGS AND PRECAUTIONS, Cardiovascular; DOSAGE AND ADMINISTRATION**).

### ***Hyperlipidemia***

Monitor serum cholesterol and triglycerides before initiating LORBRENA, 2, 4, and 8 weeks, after initiating LORBRENA, and periodically thereafter (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism; DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS**).

## **6.1 Special Populations**

### **6.1.1 Pregnant Women**

Studies in animals have shown embryo-fetal toxicity (see **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.

### 6.1.2 Breast-feeding

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.

### 6.1.3 Pediatrics

The safety and efficacy of LORBRENA in pediatric patients have not been established.

### 6.1.4 Geriatrics

Among patients from Study B7461001 who received LORBRENA 100 mg (n=295), 241 patients were < 65 years and 54 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 **ACTION AND CLINICAL PHARMACOLOGY**). Although data are limited, no clinically relevant differences in safety or efficacy were observed between patients aged greater than or equal to 65 years and younger patients.

## NOC/c 7 ADVERSE REACTIONS

### 7.1 Adverse Reaction Overview

The data in Warnings and Precautions reflect exposure to LORBRENA (lorlatinib) in 332 patients with ALK-positive or cros oncogene 1 (ROS1) positive, metastatic non-small cell lung cancer (NSCLC) enrolled in a multi-cohort, multinational, non-comparative, dose-finding, and activity-estimating trial (Study B7461001) who received LORBRENA at doses ranging from 10 mg to 200 mg daily in single or divided doses.

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

The most common (≥ 20%) laboratory abnormalities were hypercholesterolemia, hypertriglyceridemia, anemia, creatinine increased, hyperglycemia, hypoalbuminemia, AST elevations, lymphopenia, ALP elevations, ALT elevations, lipase increased, amylase increased,

hypomagnesemia, platelet count decreased, hypophosphatemia, hyponatremia, and hyperkalemia.

Serious adverse reactions were reported in 18 patients (6.1%). The most frequent serious adverse reactions reported were mental status changes in 4 patients (1.4%) and cognitive effects in 3 patients (1.0%).

Dose reductions associated with adverse reactions occurred in 76 patients (25.8%) receiving LORBRENA. The most common adverse reactions that led to dose reductions were edema in 18 patients (6.1%) and peripheral neuropathy in 14 patients (4.7%). Permanent discontinuations associated with adverse reactions occurred in 8 patients (2.7%) receiving LORBRENA. The most frequent adverse reaction that led to a permanent discontinuation were hallucinations in 2 patients (0.7%), cognitive effects in 2 patients (0.7%), and mood effects in 2 patients (0.7%). Temporary discontinuations associated with adverse reactions occurred in 103 (34.9%) patients receiving LORBRENA. The most frequent adverse reaction that led to a temporary discontinuation were edema in 17 patients (5.8%), hypertriglyceridemia in 17 patients (5.8%), and peripheral neuropathy in 15 patients (5.1%).

## 7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 3 summarizes adverse reactions in patients treated with LORBRENA.

**Table 3. Adverse Reactions Reported in ≥ 10% of Patients in Study B7461001\***

Adverse Reaction	LORBRENA (N=295)	
	All Grades n (%)	Grade 3-4 n (%)
Metabolism and nutrition disorders		
Hypercholesterolemia <sup>a</sup>	249 (84.4)	49 (16.6)
Hypertriglyceridemia <sup>b</sup>	197 (66.8)	48 (16.3)
Psychiatric disorders		
Mood effects <sup>c</sup>	65 (22.0)	5 (1.7)
Nervous system disorders		
Peripheral neuropathy <sup>d</sup>	140 (47.5)	8 (2.7)
Cognitive effects <sup>e</sup>	80 (27.1)	6 (2.0)
Headache	52 (17.6)	2 (0.7)
Dizziness	48 (16.3)	2 (0.7)
Speech effects <sup>f</sup>	34 (11.5)	1 (0.3)
Sleep effects <sup>g</sup>	29 (9.8)	0
Respiratory		
Dyspnea	79 (26.8)	16 (5.4)
Cough	54 (18.3)	0

**Table 3. Adverse Reactions Reported in ≥ 10% of Patients in Study B7461001\***

Adverse Reaction	LORBRENA (N=295)	
	All Grades n (%)	Grade 3-4 n (%)
Eye disorders Vision disorder <sup>h</sup>	43 (14.6)	1 (0.3)
Gastrointestinal disorders Diarrhea Nausea Constipation Vomiting	64 (21.7) 52 (17.6) 45 (15.3) 34 (11.5)	2 (0.7) 2 (0.7) 0 3 (1.0)
Musculoskeletal and connective tissue disorders Arthralgia Myalgia <sup>i</sup> Back pain Pain in extremity	67 (22.7) 50 (16.9) 38 (12.9) 39 (13.2)	2 (0.7) 0 2 (0.7) 1 (0.3)
General disorders and administration site conditions Edema <sup>j</sup> Fatigue <sup>k</sup> Pyrexia	159 (53.9) 76 (25.8) 36 (12.2)	7 (2.4) 1 (0.3) 2 (0.7)
Infections Upper respiratory tract infection <sup>l</sup>	36 (12.2)	0
Skin and subcutaneous tissue disorders Rash <sup>m</sup>	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

<sup>a</sup> Hypercholesterolemia (including blood cholesterol increased, hypercholesterolemia).

<sup>b</sup> Hypertriglyceridemia including (blood triglycerides increased, hypertriglyceridemia).

<sup>c</sup> 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).

<sup>d</sup> 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).

<sup>e</sup> 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).

<sup>f</sup> Speech effects (including aphasia, dysarthria, slow speech, speech disorder)



<sup>g</sup> Sleep effects (including abnormal dreams, insomnia, nightmare, sleep disorder, sleep talking, somnambulism)

<sup>h</sup> Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).

<sup>i</sup> Myalgia (including musculoskeletal pain, myalgia).

<sup>j</sup> Edema (including edema, edema peripheral, eyelid edema, face edema, generalized edema, localized edema, periorbital edema, peripheral swelling, swelling).

<sup>k</sup> Fatigue (including asthenia, fatigue).

<sup>l</sup> Upper respiratory infection (including fungal upper respiratory infection, upper respiratory infection, viral upper respiratory infection).

<sup>m</sup> Rash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash).

## Hypercholesterolemia/Hypertriglyceridemia

In B7461001, adverse reactions of increase in serum cholesterol or triglycerides were reported in 249 patients (84.4%) and 197 patients (66.8%) of patients, respectively. Mild or moderate adverse reactions of hypercholesterolemia or hypertriglyceridemia occurred in 200 (67.8%) and 149 (50.5%) patients, respectively (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**). No patient was discontinued from treatment with lorlatinib due to hypercholesterolemia or hypertriglyceridemia. The median time to onset for both hypercholesterolemia and hypertriglyceridemia was 15 days. The median duration of hypercholesterolemia and hypertriglyceridemia was 323 and 344 days, respectively.

## Nervous system disorders

In B7461001, CNS reactions were primarily cognitive effects reported in 80 patients (27.1%), mood effects in 65 patients (22.0%), and speech effects in 28 patients (9.5%), and were generally mild, transient, and reversible upon dose delay and/or dose reduction (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**). The most common cognitive effect of any grade was memory impairment reported in 33 patients (11.2%). The most common mood effect of any grade was irritability, reported in 18 patients (6.1%). The most common speech effect of any grade was dysarthria reported in 11 patients (3.7%). Median time to onset for cognitive, mood, and speech effects was 81, 43, and 42 days, respectively. Median duration of cognitive, mood, and speech effects was 194, 73, and 99 days, respectively.

## 7.3 Less Common Clinical Trial Adverse Reactions

Additional clinically significant adverse reactions occurring at an overall incidence between 1% and 10% in patients treated with LORBRENA included speech effects in 28 patients (9.5%), hallucinations in 21 patients (7%), which include hallucination, hallucination auditory and hallucination visual, mental status changes in 5 patients (1.7%), and pneumonitis in 4 patients (1.4%), which include interstitial lung disease and pneumonitis.

## 7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 4 summarizes laboratory abnormalities in patients treated with LORBRENA.

**Table 4. Worsening Laboratory Values Occurring in ≥20% of Patients in Study B7461001\***

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

<sup>a</sup> N=292.

<sup>b</sup> N=293.

<sup>c</sup> N=291.

<sup>d</sup> N=290.

<sup>e</sup> N=284.

## 7.5 Clinical Trial Adverse Reactions (Pediatrics)

Not applicable.

## 7.6 Post-Market Adverse Reactions

Not applicable.

## 8 DRUG INTERACTIONS

### 8.1 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.

### 8.2 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 **DOSAGE AND ADMINISTRATION**).

#### 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 **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**). The effect of the concomitant use of moderate CYP3A inducers on lorlatinib pharmacokinetics or the risk of hepatotoxicity with the concomitant use of moderate CYP3A inducers is unknown. 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. Avoid concomitant use with moderate CYP3A inducers, as they may also reduce lorlatinib plasma concentrations.

#### Proton-Pump inhibitors, H<sub>2</sub>-receptor antagonists, or locally acting antacids

The proton-pump inhibitor rabeprazole had a minimal effect on lorlatinib plasma exposure (90% CI for the AUC<sub>inf</sub> ratio, expressed as a percentage: 97.6%, 104.3%).

No dose adjustment is required when lorlatinib is taken with proton-pump inhibitors, H<sub>2</sub>-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 AUC<sub>inf</sub> by 64% and C<sub>max</sub> 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 C<sub>max</sub> 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-glucuronosyltransferase (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.

## **8.3 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<sub>inf</sub> and 9% lower C<sub>max</sub> (AUC<sub>inf</sub> ratio of 104.7%; 90% CI for the ratio: 101.3%, 108.3%; C<sub>max</sub> 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.

## **8.4 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 **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**). Avoid concomitant use with herbal products that are moderate CYP3A inducers, if possible, as they may also reduce lorlatinib plasma concentrations.

# **NOC/c 9 ACTION AND CLINICAL PHARMACOLOGY**

## **9.1 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.

## **9.2 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 orthotopic EML4-ALK or EML4-ALK<sup>L1196M</sup> 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  $\geq$ 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 **DOSAGE AND ADMINISTRATION**).

### **9.3 Pharmacokinetics**

**Absorption:** In patients with cancer, peak lorlatinib concentrations in plasma are rapidly reached with the median  $T_{max}$  of 1.2 hours 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  $\alpha$ 1-acid glycoprotein.

The geometric mean (geometric %CV) steady state volume of distribution (V<sub>ss</sub>) of lorlatinib was 305 (28) L following 50 mg IV administration to healthy subjects. In patients with cancer, the geometric mean (geometric %CV) V<sub>z</sub>/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.

**Geriatrics:** Of the 295 patients in safety population in B7461001, 18.3% 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. Although data are limited, no clinically relevant differences in safety or efficacy were observed between patients aged greater than or equal to 65 years and younger patients (see **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  $>2.5 \times$  ULN, or if due to underlying malignancy,  $>5.0 \times$  ULN or with total bilirubin  $>1.5 \times$  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 **DOSAGE AND ADMINISTRATION**). LORBRENA has not been studied in patients with moderate or severe hepatic impairment.

**Renal Insufficiency:** Less than 1% of the administered dose is detected as unchanged lorlatinib in urine. Clinical studies excluded patients with serum creatinine  $>1.5 \times$  ULN or estimated CL<sub>cr</sub>  $<60$  mL/min. Population pharmacokinetic analyses have shown that lorlatinib steady state exposure was not clinically meaningfully altered in patients with mild (n=103, CL<sub>cr</sub>: 60-89 mL/min) or moderate renal impairment (n=41, CL<sub>cr</sub>: 30-59 mL/min). No dose adjustments are recommended for patients with mild or moderate renal impairment (see **DOSAGE AND ADMINISTRATION**). Information for lorlatinib use in patients with severe renal impairment (n=1, CL<sub>cr</sub>  $<30$  mL/min) is limited.

## **10 STORAGE, STABILITY AND DISPOSAL**

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

## **11 SPECIAL HANDLING INSTRUCTIONS**

LORBRENA does not require any special handling instructions.



## PART II: SCIENTIFIC INFORMATION

LORBRENA (lorlatinib) is indicated as 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. *Patients should be advised of the nature of the authorization. For further information for LORBRENA please refer to Health Canada's Notice of Compliance with conditions - drug products web site:*  
<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>

### 12 PHARMACEUTICAL INFORMATION

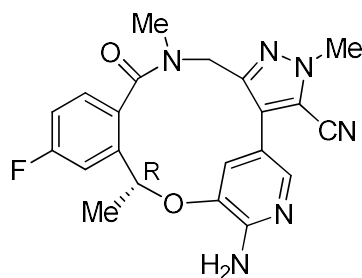
#### Drug Substance

Proper/Common name: 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: C<sub>21</sub>H<sub>19</sub>FN<sub>6</sub>O<sub>2</sub>; 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.

### NOC/c 13 CLINICAL TRIALS

#### 13.1 Trial Design and Study Demographics

The use of LORBRENA (lorlatinib) 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 5 presents an overview of the patients in the different cohorts, pooled cohorts, and their respective sizes in the Phase 2 study portion.

**Table 5. Efficacy Cohorts of ALK-Positive NSCLC Patients Assessed by ICR (Phase 2)**

<b>Study Portion</b>	<b>Cohort Name</b>	<b>Cohort Description</b>	<b>Total Number of Patients n</b>	<b>Patients with Brain Metastases at Baseline n</b>
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
	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 B7461001 are included in Tables 6 and 7.

**Table 6. Efficacy Results in B7461001**

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

<sup>a</sup> Per ICR.

<sup>b</sup> Using exact method based on binomial distribution.

<sup>c</sup> Using the Brookmeyer Crowley method.

**Table 7. Intracranial Efficacy Results in B7461001\***

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

<sup>a</sup> Per ICR.

<sup>b</sup> Using exact method based on binomial distribution.

<sup>c</sup> 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).

## 14 NON-CLINICAL TOXICOLOGY

### Repeat-dose Toxicity

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.

### 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 aneugenecity was approximately 16.5 times human clinical exposure at 100 mg based on AUC.

### Carcinogenicity

Carcinogenicity studies have not been conducted with lorlatinib.

### Reproductive Toxicity

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 embryoletality, 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.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**  
**PATIENT MEDICATION INFORMATION**

**LORBRENA™**  
**Lorlatinib tablets**

Read this carefully before you start taking LORBRENA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about LORBRENA

**What is LORBRENA used for?**

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. LORBRENA is used if your cancer has spread to other parts of your body and:

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

Read the boxed message below for more information.

LORBRENA is not approved for use in children.

For the following indication LORBRENA has been approved *with conditions* (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

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. LORBRENA is used if your cancer has spread to other parts of your body and:

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

**What is a Notice of Compliance with Conditions (NOC/c)?**

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

### Serious Warnings and Precautions

**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.

### How does LORBRENA work?

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.

### What are the ingredients in LORBRENA?

Medicinal ingredients: lorlatinib

Non-medicinal ingredients: dibasic calcium phosphate anhydrous, ferrousferic 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 forms:

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 liver problems;
- have any other medical conditions;
- 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 (cholesterol or triglycerides):**
  - 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 week, 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 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 and mental health problems:** LORBRENA can cause problems with thinking (such as forgetfulness or confusion), trouble with speech, mood changes and hallucinations (seeing and hearing things that are not real). If you experience any problems with thinking, trouble with your speech, changes in your mood or hallucinations while you are taking LORBRENA, contact your healthcare professional immediately. 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 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.

### **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;
- 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 adult dose:**

The recommended dose is 100 mg taken orally once daily.

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 have taken too much LORBRENA contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no 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.

### **What are possible side effects from using LORBRENA?**

These are not all the possible side effects you may feel when taking LORBRENA. If you experience any side effects not listed here, contact 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.

LORBRENA can cause abnormal blood test results, including high blood lipid levels. Your healthcare professional will decide when to perform blood tests and will interpret the results.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>VERY COMMON</b> <b>Changes in mental status and speech problems:</b> confusion, memory loss, trouble with attention, difficulty speaking, such as slurred or slow speech		X	
<b>Mental health problems:</b> changes in mood, irritability, agitation, mood swings, anxiety, depression, hallucinations (seeing or hearing things that aren't real)		X	
<b>Edema:</b> swelling of the legs, ankles, feet and hands		X	
<b>Vision problems:</b> double vision, sensitivity to light, blurred vision, vision loss, floaters, flashes of light		X	
<b>Liver problems</b> if it is taken with other medicines: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		X	
<b>COMMON</b> <b>Lung problems:</b> new or worsening lung problems, trouble breathing, shortness of breath, cough, or fever		X	
<b>Heart problems:</b> feel dizzy or faint or have very slow or abnormal heartbeats		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, talk to 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](https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) 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 this Patient Medication Information by visiting the [Health Canada website](http://www.canada.ca/en/health-canada.html) (<http://www.canada.ca/en/health-canada.html>); the manufacturer's website (<http://www.Pfizer.ca>), or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC

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