

LORBRENA

Lorlatinib

25 mg and 100 mg Film-coated Tablets

Reference Market: United States

AfME Markets using same as LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lorbrena 25 mg film-coated tablets
Lorbrena 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lorbrena 25 mg film-coated tablets

Each film-coated tablet contains 25 mg of lorlatinib.

Excipient with known effect
Each film-coated tablet contains 1.58 mg of lactose monohydrate.

Lorbrena 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of lorlatinib.

Excipient with known effect
Each film-coated tablet contains 4.20 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Lorbrena 25 mg film-coated tablets

Round (8 mm) tan immediate release film-coated tablet, debossed with “Pfizer” on one side and “25” and “LLN” on the other side.

Lorbrena 100 mg film-coated tablets

Oval (8.5 × 17 mm) lavender immediate release film-coated tablet, debossed with “Pfizer” on one side and “LLN 100” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LORBRENA is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA approved test

4.2 Posology and method of administration

Patient Selection

Select patients for the treatment of metastatic NSCLC with LORBRENA based on the presence of ALK positivity in tumor specimens *[see 4.1 Therapeutic indications and 5.1 Pharmacodynamic properties]*.

Recommended Dosage

The recommended dosage of LORBRENA is 100 mg orally once daily, with or without food, until disease progression or unacceptable toxicity *[see 5.2 Pharmacokinetic properties]*.

Swallow tablets whole. Do not chew, crush or split tablets. Do not ingest if tablets are broken, cracked, or otherwise not intact.

Take LORBRENA at the same time each day. If a dose is missed, then take the missed dose unless the next dose is due within 4 hours. Do not take 2 doses at the same time to make up for a missed dose.

Do not take an additional dose if vomiting occurs after LORBRENA but continue with the next scheduled dose.

Dosage Modifications for Adverse Reactions

The recommended dose reductions are:
- First dose reduction: LORBRENA 75 mg orally once daily
- Second dose reduction: LORBRENA 50 mg orally once daily

Permanently discontinue LORBRENA in patients who are unable to tolerate 50 mg orally once daily.

Dosage modifications for adverse reactions of LORBRENA are provided in Table 1.

Table 1 Recommended LORBRENA Dosage Modifications for Adverse Reactions

Adverse Reaction[a]	**Dosage Modifications**
Central Nervous System Effects *[see 4.4 Special warnings and precautions for use]*	
Grade 1	Continue at the same dose or withhold the dose until recovery to baseline. Resume LORBRENA at the same dose or at a reduced dose.
Grade 2 OR Grade 3	Withhold dose until Grade 0 or 1. Resume LORBRENA at a reduced dose.
Grade 4	Permanently discontinue LORBRENA.
Hyperlipidemia *[see 4.4 Special warnings and precautions for use]*	
Grade 4 hypercholesterolemia OR Grade 4 hypertriglyceridemia	Withhold LORBRENA until recovery of hypercholesterolemia and/or hypertriglyceridemia to less than or equal to Grade 2. Resume LORBRENA at the same dose. If severe hypercholesterolemia and/or hypertriglyceridemia recurs, resume LORBRENA at a reduced dose.
Atrioventricular (AV) Block *[see 4.4 Special warnings and precautions for use]*	
Second-degree AV block	Withhold LORBRENA until PR interval is less than 200 ms. Resume LORBRENA at a reduced dose.
First occurrence of complete AV block	Withhold LORBRENA until • pacemaker placed OR • PR interval less than 200 ms. If a pacemaker is placed, resume LORBRENA at the same dose. If no pacemaker is placed, resume LORBRENA at a reduced dose.
Recurrent complete AV block	Place pacemaker or permanently discontinue LORBRENA.
Interstitial Lung Disease (ILD)/Pneumonitis *[see 4.4 Special warnings and precautions for use]*	
Any Grade treatment–related ILD/Pneumonitis	Permanently discontinue LORBRENA.

Table 1 Recommended LORBRENA Dosage Modifications for Adverse Reactions

Adverse Reaction[a]	**Dosage Modifications**
Hypertension *[see 4.4 Special Warnings and Precautions for use]*	
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 *[see 4.4 Special Warnings and Precautions for use]*	
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.
Other Adverse Reactions	
Grade 1 OR Grade 2	Continue LORBRENA at same dose or reduced dose.
Grade 3 OR Grade 4	Withhold LORBRENA until symptoms resolve to less than or equal to Grade 2 or baseline. Resume LORBRENA at reduced dose.

Abbreviation: AV=atrioventricular; DBP=diastolic blood pressure; SBP=systolic blood pressure.
[a] Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Dosage Modifications for Drug Interactions

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. *[see 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction,5.2 Pharmacokinetic properties]*.

Moderate CYP3A Inducers

Avoid concomitant use of moderate CYP3A inducers with LORBRENA. If concomitant use with moderate CYP3A inducers is unavoidable, increase the LORBRENA dose to 125 mg once daily *[see 4.5 Interaction with other medicinal products and other forms of interaction, 5.2 Pharmacokinetic properties]*.

Strong CYP3A Inhibitors

Avoid concomitant use of LORBRENA with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor is unavoidable, reduce the starting dose of LORBRENA from 100 mg orally once daily to 75 mg orally once daily.

In patients who have had a dose reduction to 75 mg orally once daily due to adverse reactions and who initiate a strong CYP3A inhibitor, reduce the LORBRENA dose to 50 mg orally once daily.

If concomitant use of a strong CYP3A inhibitor is discontinued, increase the LORBRENA dose (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor *[see 4.5 Interaction with other medicinal products and other forms of interaction ,5.2 Pharmacokinetic properties]*.

Fluconazole

Avoid concomitant use of LORBRENA with fluconazole *[see Clinical Pharmacology (12.3)]*. If concomitant use is unavoidable, reduce the starting dose of LORBRENA from 100 mg orally once daily to 75 mg orally once daily *[see 4.5 Interaction with other medicinal products and other forms of interaction, 5.2 Pharmacokinetic properties]*.

Recommended Dosage for Severe Hepatic Impairment

The recommended dosage of LORBRENA for patients with severe hepatic impairment (Child-Pugh C) is 50 mg orally once daily *[see 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties]*.

Recommended Dosage for Renal Impairment

The recommended dosage of LORBRENA for patients with creatinine clearance [CL_{cr}] 15 to < 30 mL/min (estimated by Cockcroft-Gault) is 75 mg orally once daily *[see 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties]*.

4.3 Contraindications

LORBRENA is contraindicated in patients taking strong CYP3A inducers, due to the potential for serious hepatotoxicity *[see 4.4 Special warnings and precautions for use]*.

4.4 Special warnings and precautions for use

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 50% of subjects, Grade 3 ALT or AST elevations occurred in 33% and Grade 2 ALT or AST elevations occurred in 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 *[see 4.5 Interaction with other medicinal products and other forms of interaction]*.

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 *[see 4.3 Contraindications, 4.5 Interaction with other medicinal products and other forms of interaction]*.

Central Nervous System Effects

A broad spectrum of central nervous system (CNS) effects can occur in patients receiving LORBRENA. These include seizures, psychotic effects and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep. Overall, CNS effects occurred in 52% of the 476 patients who received 100 mg LORBRENA once daily in clinical trials *[see 4.8 undesirable effects]*. Cognitive effects occurred in 28% of the 476 patients; 2.9% of these events were severe (Grade 3 or 4). Mood effects occurred in 21% of patients; 1.7% of these events were severe. Speech effects occurred in 11% of patients; 0.6% of these events were severe. Psychotic effects occurred in 7% of patients; 0.6% of these events were severe. Mental status changes occurred in 1.3% of patients; 1.1% of these events were severe. Seizures occurred in 1.9% of patients, sometimes in conjunction with other neurologic findings. Sleep effects occurred in 12% of patients. The median time to first onset of any CNS effect was 1.4 months (1 day to 3.4 years). Overall, 2.1% of patients

required permanent discontinuation of LORBRENA for a CNS effect; 10% required temporary discontinuation and 8% required dose reduction.

Withhold and resume at the same dose or at a reduced dose or permanently discontinue LORBRENA based on severity *[see 4.2 Posology and methods of administration]*.

Hyperlipidemia

Increases in serum cholesterol and triglycerides can occur in patients receiving LORBRENA *[see 4.8 undesirable effects]*. Grade 3 or 4 elevations in total cholesterol occurred in 18% and Grade 3 or 4 elevations in triglycerides occurred in 19% of the 476 patients who received 100 mg LORBRENA once daily. The median time to onset was 15 days for both hypercholesterolemia and hypertriglyceridemia. Approximately 4% and 7% of patients required temporary discontinuation and 1% and 3% of patients required dose reduction of LORBRENA for elevations in cholesterol and in triglycerides. in Study B7461001 and Study B7461006, respectively. Eighty-three percent of patients required initiation of lipid-lowering medications, with a median time to onset of start of such medications of 17 days.

Initiate or increase the dose of lipid-lowering agents in patients with hyperlipidemia. Monitor serum cholesterol and triglycerides before initiating LORBRENA, 1 and 2 months 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 4.2 Posology and methods of administration]*.

Atrioventricular Block

PR interval prolongation and atrioventricular (AV) block can occur in patients receiving LORBRENA *[see 4.8 undesirable effects, 5.1 Pharmacodynamic properties]*. In 476 patients who received 100 mg LORBRENA once daily and who had a baseline electrocardiography (ECG), 1.9% experienced AV block and 0.2% experienced Grade 3 AV block and underwent pacemaker placement.

Monitor ECG prior to initiating LORBRENA and periodically thereafter. Withhold and resume at a reduced dose or at the same dose in patients who undergo pacemaker placement. Permanently discontinue for recurrence in patients without a pacemaker *[see 4.2 Posology and methods of administration]*.

Interstitial Lung Disease/Pneumonitis

Severe or life-threatening pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis can occur with LORBRENA. ILD/pneumonitis occurred in 1.9% of patients who received 100 mg LORBRENA once daily, including Grade 3 or 4 ILD/pneumonitis in 0.6% of patients. 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 4.2 Posology and methods of administration]*.

Hypertension

Hypertension can occur in patients receiving LORBRENA *[see 4.8 Undesirable effects]*. Hypertension occurred in 13% of patients who received 100 mg LORBRENA once daily, including Grade 3 or 4 in 6% of patients. The median time to onset of hypertension was 6.4 months (1 day to 2.8 years), and 2.3% of patients temporarily discontinued LORBRENA for 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 4.2 Posology and method of administration]*.

Hyperglycemia

Hyperglycemia can occur in patients receiving LORBRENA *[see 4.8 Undesirable effects]*. Hyperglycemia occurred in 9% of patients who received 100 mg LORBRENA, including Grade 3 or 4 in 3.2% of patients. 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.

Assess fasting serum glucose prior to initiation of LORBRENA and monitor periodically thereafter. Withhold and resume at a reduced dose or permanently discontinue LORBRENA based on severity *[see 4.2 Posology and method of administration]*.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, LORBRENA can cause fetal harm when administered to a pregnant woman. Administration of lorlatinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in malformations, increased post-implantation loss, and abortion at maternal exposures that were equal to or less than the human exposure at the recommended dose of 100 mg once daily based on area under the curve (AUC).

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective non-hormonal method of contraception, since LORBRENA can render hormonal contraceptives ineffective, during treatment with LORBRENA and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with LORBRENA and for 3 months after the final dose *[see 4.5 Interaction with other medicinal products and other forms of interaction, 4.6 Fertility, pregnancy and lactation, 5.3 Preclinical safety data]*.

Pediatric Use

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

Geriatric Use

Of the patients in Study B7461001 (N=295) and Study B7461006 (N=149) who received 100 mg LORBRENA orally once daily, 18% and 40% of patients, 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.

Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh C), the recommended dosage of LORBRENA is 50 mg orally once daily *[see 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties]*.

No dose adjustment is recommended for patients with mild (total bilirubin ≤ ULN with AST > ULN or total bilirubin >1 to 1.5 × ULN with any AST) to moderate (Child-Pugh B) hepatic impairment *[see 5.2 Pharmacokinetic properties]*.

Renal Impairment

In patients with CL_{cr} 15 to <30 mL/min, (estimated by Cockcroft Gault), the recommended dosage of LORBRENA is 75 mg orally once daily *[see 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties]*.

No dose adjustment is recommended for patients with CL_{cr} 30 to 89 mL/min, (estimated by Cockcroft-Gault) r*[see 5.2 Pharmacokinetic properties]*.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Other Drugs on LORBRENA

Strong CYP3A Inducers
LORBRENA is contraindicated in patients taking strong CYP3A inducers *[see 4.3 Contraindication]*. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating LORBRENA *[see 4.2 Posology and method of administration]*.

Concomitant use of LORBRENA with a strong CYP3A inducer decreased lorlatinib plasma concentrations *[see 5.2 Pharmacokinetic properties]*, which may decrease the efficacy of LORBRENA.

Severe hepatotoxicity occurred in healthy subjects receiving LORBRENA with rifampin, a strong CYP3A inducer. In 12 healthy subjects receiving a single 100 mg dose of LORBRENA with multiple daily doses of rifampin, Grade 3 or 4 increases in ALT or AST occurred in 83% of subjects and Grade 2 increases in ALT or AST occurred in 8%. A possible mechanism for hepatotoxicity is through activation of the pregnane X receptor (PXR) by LORBRENA and rifampin, which are both PXR agonists.

Moderate CYP3A Inducers
Avoid concomitant use of moderate CYP3A inducers with LORBRENA. If concomitant use is unavoidable, increase the LORBRENA dose *[see 4.2 Posology and method of administration]*.

Concomitant use of LORBRENA with a moderate CYP3A inducer decreased lorlatinib plasma concentrations, which may decrease the efficacy of LORBRENA *[see 5.2 Pharmacokinetic properties]*.

Strong CYP3A Inhibitors
Avoid the concomitant use of LORBRENA with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce the LORBRENA dosage *[see 4.2 Posology and method of administration, 5.2Pharmacokinetic properties]*.

Concomitant use with a strong CYP3A inhibitor increased lorlatinib plasma concentrations *see 5.2 Pharmacokinetic properties]* which may increase the incidence and severity of adverse reactions of LORBRENA.

Fluconazole
Avoid concomitant use of LORBRENA with fluconazole. If concomitant use cannot be avoided, reduce the LORBRENA dosage *[see 4.2 Posology and method of administration]*.

Concomitant use of LORBRENA with fluconazole may increase lorlatinib plasma concentrations *[see 5.2 Pharmacokinetic properties]*, which may increase the incidence and severity of adverse reactions of LORBRENA.

Effect of LORBRENA on Other Drugs

Certain CYP3A Substrates
Avoid concomitant use of LORBRENA with certain CYP3A substrates, for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with approved product labeling.

LORBRENA is a moderate CYP3A inducer. Concomitant use of LORBRENA decreases the concentration of CYP3A substrates *[see 5.2 Pharmacokinetic properties]*, which may reduce the efficacy of these substrates.

Certain P-glycoprotein (P-gp) Substrates
Avoid concomitant use of LORBRENA with certain P-gp substrates for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the P-gp substrate dosage in accordance with approved product labeling.

LORBRENA is a moderate P-gp inducer. Concomitant use of LORBRENA decreases the concentration of P-gp substrates *[see 5.2 Pharmacokinetic properties]*, which may reduce the efficacy of these substrates.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see 5.1 Pharmacodynamic properties]*, LORBRENA can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on LORBRENA use in pregnant women. Administration of lorlatinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in malformations, increased post-implantation loss, and abortion at maternal exposures that were equal to or less than the human exposure at the recommended dose of 100 mg once daily based on AUC *(see Data)*. Advise a pregnant woman of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data

Animal Data
Preliminary embryo-fetal development studies investigating the administration of lorlatinib during the period of organogenesis were conducted in rats and rabbits. In rabbits, lorlatinib administration resulted in abortion and total loss of pregnancy at doses of 15 mg/kg (approximately 3 times the human exposure at the recommended dose of 100 mg) or greater. At a dose of 4 mg/kg (approximately 0.6 times the human exposure at the recommended dose of 100 mg) toxicities included increased post-implantation loss and malformations including rotated limbs, malformed kidneys, domed head, high arched palate, and dilation of the cerebral ventricles. In rats, administration of lorlatinib resulted in total loss of pregnancy at doses of 4 mg/kg (approximately 5 times the human exposure at the recommended dose of 100 mg) or greater. At a dose of 1 mg/kg (approximately equal to the human exposure at the recommended dose of 100 mg) there was increased post-implantation loss, decreased fetal body weight, and malformations including gastroschisis, rotated limbs, supernumerary digits, and vessel abnormalities.

Lactation

Risk Summary
There are no data on the presence of lorlatinib or its metabolites in either human or animal milk or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants, instruct women not to breastfeed during treatment with LORBRENA and for 7 days after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating LORBRENA

Contraception
LORBRENA can cause embryo-fetal harm when administered to a pregnant woman

Females
Advise female patients of reproductive potential to use effective non-hormonal contraception during treatment with LORBRENA and for at least 6 months after the final dose. Advise females of reproductive potential to use a non-hormonal method of contraception, because LORBRENA can render hormonal contraceptives ineffective *[see 4.5 Interaction with other medicinal products and other forms of interaction]*.

Males
Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with LORBRENA and for at least 3 months after the final dose *[see 5.3 Preclinical safety data]*.

Infertility

Males
Based on findings from animal studies, LORBRENA may transiently impair male fertility *[see 5.3 Preclinical safety data]*.

4.7 Effects on ability to drive and use machines

Lorlatinib has moderate influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience CNS effects (see Section 4.8).

4.8 Undesirable effects

The following adverse reactions are described elsewhere in the labeling:

- Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers *[see 4.4 Special warnings and precautions for use]*
- Central Nervous System Effects *[see 4.4 Special warnings and precautions for use]*
- Hyperlipidemia *[see 4.4 Special warnings and precautions for use]*
- Atrioventricular Block *[see 4.4 Special warnings and precautions for use]*
- Interstitial Lung Disease/Pneumonitis *[see 4.4 Special warnings and precautions for use]*
- Hypertension *[see 4.4 Special Warnings and Precautions for use]*
- Hyperglycemia *[see 4.4 Special Warnings and Precautions for use]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the 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%). 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 NSCLC (CROWN Study)

The safety of LORBRENA was evaluated in 149 patients with ALK-positive NSCLC in a randomized, open-label, active-controlled trial for the treatment of patients with ALK-positive, locally advanced or metastatic, NSCLC who had not received previous systemic treatment for advanced disease *[see 5.1 Pharmacodynamic properties]*. 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.

Serious adverse reactions occurred in 34% of patients treated with LORBRENA; the most frequently reported serious adverse reactions were pneumonia (4.7%), dyspnea (2.7%), respiratory failure (2.7%), cognitive effects (2.0%), and pyrexia (2.0%). Fatal adverse reactions occurred in 3.4% of patients treated with LORBRENA and included pneumonia (0.7%), respiratory failure (0.7%), cardiac failure acute (0.7%), pulmonary embolism (0.7%), and sudden death (0.7%).

Permanent discontinuation of LORBRENA due to adverse reactions occurred in 6.7% of patients. The most frequent adverse reaction that led to permanent discontinuation of LORBRENA was cognitive effects (1.3%). Adverse reactions leading to dose interruptions occurred in 49% of patients treated with LORBRENA. The

most frequent adverse reactions that led to dose interruptions of LORBRENA were hypertriglyceridemia (7%), edema (5%), pneumonia (4.7%) cognitive effects (4.0%), mood effects (4.0%), and hypercholesterolemia (3.4%). Adverse reactions leading to dose reductions occurred in 21% of patients treated with LORBRENA. The most frequent adverse reactions that led to dose reductions were edema (5%), hypertriglyceridemia (4.0%), and peripheral neuropathy (3.4%).

Tables 2 and 3 summarize most frequent adverse reactions and laboratory abnormalities, respectively, in patients treated with LORBRENA in Study B7461006.

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

Adverse Reaction	LORBRENA N=149		Crizotinib N=142	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Psychiatric				
Mood effects[a]	16	2	5	0
Nervous system				
Peripheral neuropathy[b]	34	2	15	0.7
Cognitive effects[c]	21	2	6	0
Headache	17	0	18	0.7
Dizziness	11	0	14	0
Sleep effects[d]	11	1.3	10	0
Respiratory				
Dyspnea	20	2.7	16	2.1
Cough	16	0	18	0
Respiratory failure	2.7	2	0	0
Vascular disorders				
Hypertension	18	10	2.1	0
Ocular				
Vision disorder[e]	18	0	39	0.7
Gastrointestinal				
Diarrhea	21	1.3	52	0.7
Nausea	15	0.7	52	2.1
Constipation	17	0	30	0.7
Vomiting	13	0.7	39	1.4
Musculoskeletal and connective tissue				
Arthralgia	19	0.7	11	0
Myalgia[f]	15	0.7	7	0
Back pain	15	0.7	11	0
Pain in extremity	17	0	8	0
General				
Edema[g]	56	4	40	1.4
Weight gain	38	17	13	2.1
Fatigue[h]	19	1.3	32	2.8
Pyrexia	17	1.3	13	1.4
Chest pain	11	1.3	14	0.7
Infections				
Upper respiratory tract infection[i]	11	0.7	7.7	1.4
Pneumonia	7.4	2	8.5	3.5
Bronchitis	6.7	2	2.1	0
Skin				
Rash[j]	11	0	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.

Adverse Reaction	LORBRENA N=149		Crizotinib N=142	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)

[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).
[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).

Additional clinically significant adverse reactions occurring at an incidence between 1% and 10% were speech effects (6.7%) and psychotic effects (3.4%).

Table 3 Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in Study B7461006

Laboratory Abnormality	LORBRENA N=149		Crizotinib N=142	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Hypertriglyceridemia[a,A]	95	22	27	0
Hypercholesterolemia[a,A]	91	19	12	0
Increased creatinine[a,A]	81	0.7	99	2.1
Increased GGT[a,A]	52	6	41	6
Increased AST[a,A]	48	2	75	3.5
Hyperglycemia[a,A]	48	7	27	2.1
Increased ALT[a,A]	44	2.7	75	4.3
Increased CPK[a,A]	39	2	64	5
Hypoalbuminemia[a,A]	36	0.7	61	6
Increased lipase[a,A]	28	7	34	5
Increased alkaline phosphatase[a,A]	23	0	50	0.7
Hyperkalemia[a,A]	21	1.3	27	2.1
Increased amylase[b,A]	20	1.4	32	1.4
Hematology				
Anemia[a,A]	48	2	38	2.8
Activated PTT[c,B]	25	0	14	0
Lymphopenia[a,A]	23	2.7	43	6
Thrombocytopenia[a,A]	23	0	7	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).

Previously Treated ALK-Positive Metastatic NSCLC

The data described below reflect exposure to LORBRENA in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORBRENA 100 mg orally once daily in Study B7461001, a multi-cohort, non-comparative trial *[see 5.1 Pharmacological properties]*. The median duration of exposure to LORBRENA was 12.5 months (1 day to 35 months) and 52% received LORBRENA for ≥12 months. Patient characteristics were a median age of 53 years (19 to 85 years), age ≥65 years (18%), female (58%), White (49%), Asian (37%), and ECOG performance status 0 or 1 (96%).

The most frequent (≥20%) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, 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, increased lipase, and increased alkaline phosphatase.

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

The most frequent adverse reactions that led to permanent discontinuation were respiratory failure (1.4%), dyspnea (0.7%), myocardial infarction (0.7%), cognitive effects (0.7%) and mood effects (0.7%). Approximately 48% of patients required dose interruption. The most frequent adverse reactions that led to dose interruptions were edema (7%), hypertriglyceridemia (6%), peripheral neuropathy (5%), cognitive effects (4.4%), increased lipase (3.7%), hypercholesterolemia (3.4%), mood effects (3.1%), dyspnea (2.7%), pneumonia (2.7%), and hypertension (2.0%). Approximately 24% of patients required at least 1 dose reduction for adverse reactions. The most frequent adverse reactions that led to dose reductions were edema (6%), peripheral neuropathy (4.7%), cognitive effects (4.1%), and mood effects (3.1%).

Tables 4 and 5 summarize most frequent adverse reactions and laboratory abnormalities, respectively, in patients treated with LORBRENA in Study B7461001.

Table 4 Adverse Reactions Occurring in ≥10% of Patients in Study B7461001*

Adverse Reaction	LORBRENA (N=295)	
	All Grades (%)	Grade 3 or 4 (%)
Psychiatric		
Mood effects[a]	23	1.7
Nervous system		
Peripheral neuropathy[b]	47	2.7
Cognitive effects[c]	27	2
Headache	18	0.7
Dizziness	16	0.7
Speech effects[d]	12	0.3
Sleep effects[e]	10	0
Respiratory		
Dyspnea	27	5
Cough	18	0
Ocular		
Vision disorder[f]	15	0.3
Gastrointestinal		
Diarrhea	22	0.7
Nausea	18	0.7
Constipation	15	0
Vomiting	12	1

Table 4 Adverse Reactions Occurring in ≥10% of Patients in Study B7461001*

Adverse Reaction	LORBRENA (N=295)	
	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue		
Arthralgia	23	0.7
Myalgia[g]	17	0
Back pain	13	0.7
Pain in extremity	13	0.3
General		
Edema[h]	57	3.1
Fatigue[i]	26	0.3
Weight gain	24	4.4
Pyrexia	12	0.7
Infections		
Upper respiratory tract infection[j]	12	0
Skin		
Rash[k]	14	0.3

* 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, aggression, agitation, anxiety, depressed mood, depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress, suicidal ideation).

[b] 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).

[c] 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, disorientation, reading disorder).

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

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

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

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

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

[i] Fatigue (including asthenia, fatigue).

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

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

Additional clinically significant adverse reactions occurring at an incidence between 1% and 10% were psychotic effects (7%).

Table 5 Worsening Laboratory Values Occurring in ≥20% of Patients in Study B7461001*

Laboratory Abnormality	LORBRENA	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Hypercholesterolemia[a]	96	18
Hypertriglyceridemia[a]	90	18
Hyperglycemia[b]	52	5
Increased AST[a]	37	2.1
Hypoalbuminemia[c]	33	1
Increased ALT[a]	28	2.1
Increased lipase[d]	24	10
Increased alkaline phosphatase[a]	24	1
	22	3.9
Increased amylase[e]	21	4.8
Hypophosphatemia[a]	21	1
Hyperkalemia[b]	21	0
Hypomagnesemia[a]		
Hematology		
Anemia[b]	52	4.8
Thrombocytopenia[b]	23	0.3
Lymphopenia[a]	22	3.4

* Grades using NCI CTCAE version 4.03.
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.

Reporting of adverse reactions
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to National Pharmacovigilance Center (NPC).

To report any side effects:

- **Saudi Arabia**

National Pharmacovigilance Center (NPC)
- Call center :19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

- **Other GCC States**

- *Please contact the relevant competent authority.*

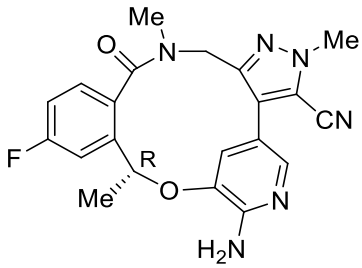
4.9 Overdose

Treatment of overdose with the medicinal product consists of general supportive measures. Given the dose-dependent effect on PR interval, ECG monitoring is recommended. There is no antidote for lorlatinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

LORBRENA (lorlatinib) is a kinase inhibitor for oral administration. The molecular formula is C21H19FN6O2 (anhydrous form) and the molecular weight is 406.41 Daltons. The chemical name is (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-4,8-methenopyrazolo[4,3-h][2,5,11] benzoxadiazacyclotetradecine-3-carbonitrile. The chemical structure is shown below:



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.

Mechanism of Action

Lorlatinib is a kinase inhibitor with in vitro activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK. Lorlatinib demonstrated in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors.

In mice subcutaneously implanted with tumors harboring EML4 fusions with either ALK variant 1 or ALK mutations, including the G1202R and I1171T mutations detected in tumors at the time of disease progression on ALK inhibitors, administration of lorlatinib resulted in antitumor activity. Lorlatinib also demonstrated anti-tumor activity and prolonged survival in mice implanted intracranially with EML4-ALK-driven tumor cell lines. The overall antitumor activity of lorlatinib in in vivo models was dose-dependent and correlated with inhibition of ALK phosphorylation.

Pharmacodynamics

Exposure-response relationships for Grade 3 or 4 hypercholesterolemia and for any Grade 3 or 4 adverse reaction were observed at steady-state exposures achieved at the recommended dosage, with higher probability of the occurrence of adverse reactions with increasing lorlatinib exposure.

Cardiac Electrophysiology

In 295 patients who received LORBRENA at the recommended dosage of 100 mg once daily and had an ECG measurement in Study B7461001, the maximum mean change from baseline for PR interval was 16.4 ms (2-sided 90% upper confidence interval [CI] 19.4 ms). Among the 284 patients with PR interval <200 ms at baseline, 14% had PR interval prolongation ≥200 ms after starting LORBRENA. The prolongation of PR interval occurred in a concentration-dependent manner. Atrioventricular block occurred in 1% of patients.

In 275 patients who received LORBRENA at the recommended dosage in the activity-estimating portion of Study B7461001, no large mean increases from baseline in the QTcF interval (i.e., >20 ms) were detected.

Clinical Studies

Previously Untreated ALK-Positive Metastatic NSCLC (CROWN Study)

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 (Study B7461006; NCT03052608). 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, at least 2 weeks (for stereotactic or partial radiation) or 4 weeks (for whole brain irradiation) 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. The major efficacy outcome measure was progression-free survival (PFS) as determined by Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1). Additional efficacy outcome measures were overall survival (OS) and tumor assessment related data by BICR, including overall response rate (ORR), and duration of response (DOR). 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) by BICR.

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 ECOG performance status at baseline was 0 or 1 in 96% of patients. The majority of patients had adenocarcinoma (95%) and never smoked (59%). CNS metastases were present in 26% (n=78) of patients: of these, 30 patients had measurable CNS lesions.

Efficacy results from Study B7461006 as assessed by BICR are summarized in Table 6 and Figure 1. Results demonstrated a significant improvement in PFS for the LORBRENA arm over the crizotinib arm. At the data cutoff point OS data was not mature.

Table 6 Efficacy Results in Study B7461006 (CROWN)

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 (Range)	NE (0.9, 31.3)	11 (1.1, 27.5)
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.

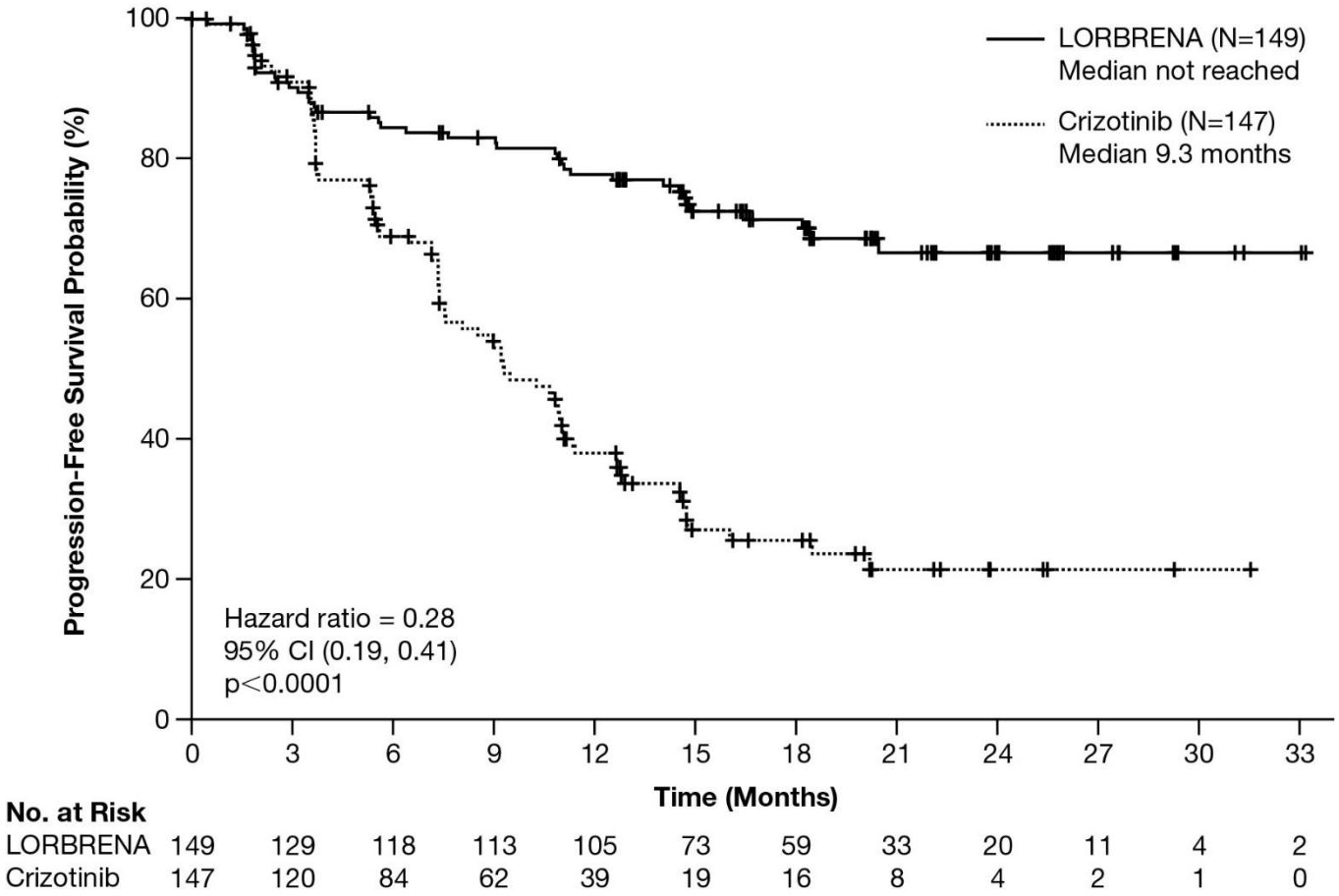
[*] p-value based on 1-sided stratified log-rank test.

[a] Based on the Brookmeyer and Crowley method.

[b] Hazard ratio based on Cox proportional hazards model.

[c] Using exact method based on binomial distribution.

Figure 1: Kaplan-Meier Plot of Progression-Free Survival by BICR in Study B7461006 (CROWN)



The results of prespecified exploratory analyses of intracranial response rate in 30 patients with measurable CNS lesions at baseline as assessed by BICR are summarized in Table 7.

Table 7 Intracranial Response Rate in Patients with Measurable Intracranial Lesions in CROWN

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.

ALK-Positive Metastatic NSCLC Previously Treated with an ALK Kinase Inhibitor

The efficacy of LORBRENA was demonstrated in a subgroup of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK kinase inhibitors who were enrolled in a non-randomized, dose-ranging and activity-estimating, multi-cohort, multicenter study (Study B7461001; NCT01970865). Patients included in this subgroup were required to have metastatic disease with at least 1 measurable target lesion according to 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), and received LORBRENA 100 mg orally once daily. 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. In addition, for patients with ALK-positive metastatic NSCLC, the extent

and type of prior treatment was specified for each individual cohort (see Table 8). The major efficacy outcome measures were ORR and intracranial ORR, according to RECIST v1.1, as assessed by Independent Central Review (ICR) committee. Data were pooled across all subgroups listed in Table 8. Additional efficacy outcome measures included DOR, and intracranial DOR.

A total of 215 patients were enrolled across the subgroups in Table 8. The distribution of patients by type and extent of prior therapy is provided in Table 8. The demographic characteristics across all 215 patients were: 59% female, 51% White, 34% Asian, and the median age was 53 years (29 to 85 years) with 18% of patients ≥65 years. The ECOG performance status at baseline was 0 or 1 in 96% of patients. All patients had metastatic disease and 95% had adenocarcinoma. Brain metastases as identified by ICR were present in 69% of patients; of these, 60% had received prior radiation to the brain and 60% (n=89) had measurable disease per ICR.

Table 8 Extent of Prior Therapy in the Subgroup of Patients with Previously Treated ALK-Positive Metastatic NSCLC in Study B7461001

Extent of prior therapy	**Number of patients**
Prior crizotinib and no prior chemotherapy[a]	29
Prior crizotinib and 1-2 lines of prior chemotherapy[a]	35
Prior ALK inhibitor (not crizotinib) with or without prior chemotherapy[a]	28
Two prior ALK inhibitors with or without prior chemotherapy[a]	75
Three prior ALK inhibitors with or without prior chemotherapy[a]	48
Total	215

Abbreviations: ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer.
[a] Chemotherapy administered in the metastatic setting.

Efficacy results for Study B7461001 are summarized in Tables 9 and 10.

Table 9 Efficacy Results in Study B7461001

Efficacy Parameter	**Overall N=215**
Overall response rate[a] (95% CI)[b]	48% (42, 55)
Complete response	4%
Partial response	44%
Duration of response	
Median, months[c] (95% CI)	12.5 (8.4, 23.7)

Abbreviations: CI=confidence interval; N=number of patients.
[a] Per Independent Central Review.
[b] Using exact method based on binomial distribution.
[c] Estimated using the Kaplan Meier method.

An assessment of intracranial ORR and the duration of response for CNS metastases in the subgroup of 89 patients in Study B7461001 with baseline measurable lesions in the CNS according to RECIST v1.1 are summarized in Table 10. Of these, 56 (63%) patients received prior brain radiation, including 42 patients (47%) who completed brain radiation treatment at least 6 months before starting treatment with LORBRENA.

Table 10 Intracranial Response Rate in Patients with Measurable Intracranial Lesions in Study B7461001

Efficacy Parameter	**Intracranial N=89**
Intracranial response rate[a] (95% CI)[b]	60% (49, 70)
Complete response	21%
Partial response	38%
Duration of response	
Median, months[c] (95% CI)	19.5 (12.4, NR)

Abbreviations: CI=confidence interval; N=number of patients; NR=not reached.
[a] Per Independent Central Review.
[b] Using exact method based on binomial distribution.

[c] Estimated using the Kaplan-Meier method.

In exploratory analyses conducted in subgroups defined by prior therapy, the response rates to LORBRENA were:

- ORR = 39% (95% CI: 30, 48) in 119 patients who received crizotinib and at least one other ALK inhibitor, with or without prior chemotherapy
- ORR = 31% (95% CI: 9, 61) in 13 patients who received alectinib as their only ALK inhibitor, with or without prior chemotherapy
- ORR = 46% (95% CI: 19, 75) in 13 patients who received ceritinib as their only ALK inhibitor, with or without prior chemotherapy

5.2 Pharmacokinetic properties

At the recommended dosage, the mean (coefficient of variation [CV] %) maximum plasma concentration (Cmax) is 577 ng/mL (42%) and the $AUC_{0\text{-}24h}$ is 5,650 ng·h/mL (39%). Steady-state lorlatinib C_{max} increases proportionally and AUC increased slightly less than proportionally over the dose range of 10 mg to 200 mg orally once daily (0.1 to 2 times the recommended dosage).

Absorption

The median lorlatinib Tmax is 1.2 hours (0.5 to 4 hours) following a single oral 100 mg dose and 2 hours (0.5 to 23 hours) following 100 mg orally once daily at steady state.
The mean absolute bioavailability is 81% (90% CI 76%, 86%).

Effect of Food

No clinically significant differences in lorlatinib pharmacokinetics were observed following administration of a high fat, high calorie meal (approximately 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat).

Distribution

Lorlatinib is 66% bound to plasma proteins, in vitro. The blood-to-plasma ratio is 0.99, in vitro.

Elimination

The mean plasma half life (t½) of lorlatinib was 24 hours (40%) after a single oral 100 mg dose of LORBRENA. The mean oral clearance (CL/F) was 11 L/h (35%) following a single oral 100 mg dose and increased to 18 L/h (39%) at steady state, suggesting autoinduction.

Metabolism

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

In plasma, a benzoic acid metabolite (M8) of lorlatinib resulting from the oxidative cleavage of the amide and aromatic ether bonds of lorlatinib accounted for 21% of the circulating radioactivity. The oxidative cleavage metabolite, M8, is pharmacologically inactive.

Excretion

Following a single oral 100 mg dose of radiolabeled lorlatinib, 48% of the radioactivity was recovered in urine (<1% as unchanged) and 41% in feces (about 9% as unchanged).

Specific Populations

No clinically significant differences in lorlatinib pharmacokinetics were observed based on age (19 to 85 years), sex, race/ethnicity (52% White, 8% Black, 27% Asian), body weight (32-156 kg), CLcr 30 to 89 mL/min, (estimated by Cockcroft-Gault), mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 × ULN and any AST) to moderate (Child-Pugh B) hepatic impairment, or metabolizer phenotypes for CYP3A5 and CYP2C19.

Patients with Moderate or Severe Hepatic Impairment
Following administration of a single oral 100 mg dose of LORBRENA, lorlatinib AUC increased 1.1-fold in non-cancer subjects with moderate hepatic impairment (Child-Pugh B) and 1.8-fold in non-cancer subjects with severe hepatic impairment (Child-Pugh C).

Patients with Renal Impairment
Following administration of a single oral 100 mg dose of LORBRENA, lorlatinib AUC increased 1.4-fold in subjects with CL_{cr} 15 to <30 mL/min(estimated by Cockcroft-Gault). The pharmacokinetics of lorlatinib have not been studied in patients with end-stage renal disease requiring hemodialysis.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A Inducers: Rifampin (a strong CYP3A inducer that also activates PXR) 600 mg once daily for 8 days (Days 1 to 8) coadministered with a single oral 100 mg dose of LORBRENA on Day 8. reduced the mean lorlatinib AUC by 85% and C_{max} by 76%. Grade 2 to 4 increases in ALT or AST occurred within 3 days. Grade 4 ALT or AST elevations occurred in 50%, Grade 3 ALT or AST elevations in 33%, and Grade 2 ALT or AST elevations occurred in 8% of subjects. ALT and AST returned to within normal limits within 7 to 34 days (median 15 days).

Moderate CYP3A Inducers: Modafinil (a moderate CYP3A inducer) decreased lorlatinib AUC by 23% and C_{max} by 22% of a single oral 100 mg dose of LORBRENA.

Strong CYP3A Inhibitors: Itraconazole (a strong CYP3A inhibitor) increased lorlatinib AUC 1.4-fold and C_{max} 1.2-fold of a single oral 100 mg dose of LORBRENA.

Fluconazole: Fluconazole is predicted to increase lorlatinib AUC 1.6-fold and C_{max} 1.3-fold following concomitant oral administration of 100 mg of LORBRENA once daily and 200 mg fluconazole once daily.

Moderate CYP3A Inhibitors: No clinically significant effect on lorlatinib pharmacokinetics is predicted when used concomitantly with verapamil or erythromycin.

CYP3A Substrates: LORBRENA 150 mg orally once daily for 15 days decreased AUC by 64% and Cmax by 50% of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate).

CYP2B6 Substrates: LORBRENA 100 mg orally once daily for 15 days decreased AUC by 25% and Cmax by 27% of a single oral 100 mg dose of bupropion (a sensitive CYP2B6 substrate).

CYP2C9 Substrates: LORBRENA 100 mg orally once daily for 15 days decreased AUC by 43% and Cmax by 15% of a single oral 100 mg dose of tolbutamide (a sensitive CYP2C9 substrate).

UGT1A Substrates: LORBRENA 100 mg orally once daily for 15 days decreased AUC by 45% and Cmax by 28% of a single oral 100 mg dose of acetaminophen (a UGT1A substrate).

P-gp Substrates: LORBRENA 100 mg orally once daily for 15 days decreased AUC by 67% and Cmax by 63% of a single oral 60 mg dose of fexofenadine (a P-gp substrate).

Acid-Reducing Agents: Concomitant use of a proton pump inhibitor, rabeprazole, did not have a clinically significant effect on lorlatinib pharmacokinetics.

In Vitro Studies

CYP Enzymes: Lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A and that it activates PXR, with the net effect in vivo being induction. Lorlatinib induces CYP2B6 and activates the human

constitutive androstane receptor (CAR). Lorlatinib and the major circulating metabolite, M8, do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, orCYP2D6. M8 does not inhibit CYP3A.

M8 does not induce CYP1A2, CYP2B6, or CYP3A.

UDP-glucuronosyltransferase (UGT): Lorlatinib and M8 do not inhibit UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15.

Transporter system: Lorlatinib is an inhibitor of P-gp and that it activates PXR (potential to induce P-gp), with the net effect in vivo being induction.

Lorlatinib inhibits OCT1, OAT3, MATE1, and intestinal BCRP. Lorlatinib does not inhibit OATP1B1, OATP1B3, OAT1, OCT2, MATE2K, or systemic BCRP. M8 does not inhibit P gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with lorlatinib. Lorlatinib was aneugenic in an in vitro assay in human lymphoblastoid TK6 cells and positive for micronuclei formation in vivo in the bone marrow of rats. Lorlatinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay.

Dedicated fertility studies were not conducted with lorlatinib. Findings in male reproductive organs occurred in repeat-dose toxicity studies and included lower testicular, epididymal, and prostate weights; testicular tubular degeneration/atrophy; prostatic atrophy; and/or epididymal inflammation at 15 mg/kg/day and 7 mg/kg/day in rats and dogs, respectively (approximately 8 and 2 times, respectively, the human exposure at the recommended dose of 100 mg based on AUC). The effects on male reproductive organs were reversible.

Animal Toxicology and/or Pharmacology

Distended abdomen, skin rash, and increased cholesterol and triglycerides occurred in animals. These findings were accompanied by hyperplasia and dilation of the bile ducts in the liver and acinar atrophy of the pancreas in rats at 15 mg/kg/day and in dogs at 2 mg/kg/day (approximately 8 and 0.5 times, respectively, the human exposure at the recommended dose of 100 mg based on AUC). All effects were reversible within the recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LORBRENA is supplied as tablets containing 25 mg or 100 mg of lorlatinib with the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate. The film-coating contains hydroxypropyl methylcellulose (HPMC) 2910/hypromellose, lactose monohydrate, macrogol/polyethylene glycol (PEG) 3350, triacetin, titanium dioxide, ferrosoferric oxide/black iron oxide, and iron oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Do not use Lorbrena after the expiry date which is stated on the Bottle after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Store LORBRENA below 30°C.

6.5 Nature and contents of container

- Lorbrena 25 mg film coated tablets:
  8 mm round, tan, immediate release, film-coated tablet, debossed with “Pfizer” on one side and “25” and “LLN” on the other side. Packed in a 30 tablets bottle with a child-resistant closure.

- Lorbrena 100 mg film coated tablets:
  8.5 mm × 17 mm oval, lavender, immediate release, film-coated tablet, debossed with “Pfizer” on one side and “LLN 100” on the other side. Packed in a 30 tablets bottle with a child-resistant closure.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER
Pfizer Inc.,
United States of America

MANUFACUTRED BY
Pfizer Manufacturing Deutschland GmbH,
Germany

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 22-July-2020
Date of latest renewal: 24-August-2025

9. DATE OF REVISION OF THE TEXT

January 2026