

**LORBRENA ®**

Lorlatinib

25 mg and 100 mg Tablets

Referenace Market: US

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) light pink 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) dark pink 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 patients with anaplastic lymphoma kinase (ALK)‑positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on

* + crizotinib and at least one other ALK inhibitor for metastatic disease; or
  + alectinib as the first ALK inhibitor therapy for metastatic disease; or
  + ceritinib as the first ALK inhibitor therapy for metastatic disease.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see 5.1 Pharmacodynamic properties]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**4.2 Posology and method of administration**

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 Reactiona** | **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. |
| **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.  a Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. | |

**Concomitant Use of Strong or Moderate 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. Avoid concomitant use of LORBRENA with moderate CYP3A inducers *[see 4.4 Special warnings and precautions for use , 5.2 Pharmacokinetic properties].*

**Dosage Modification for Strong CYP3A Inhibitors**

Avoid concomitant use of LORBRENA with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor cannot be avoided, 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 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.

LORBRENA is contraindicatedin 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. 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.

Depending upon the relative importance of each drug, discontinue LORBRENA or the CYP3A inducer for persistent Grade 2 or higher hepatotoxicity *[see 5.2 Pharmacokinetic properties]*.

**Central Nervous System Effects**

A broad spectrum of central nervous system (CNS) effects can occur in patients receiving LORBRENA. These include seizures, hallucinations, and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep. Overall, CNS effects occurred in 54% of patients receiving LORBRENA *[see 4.8 undesirable effects]*. Cognitive effects occurred in 29% of the 332 patients who received LORBRENA at any dose in Study B7461001; 2.1% of these events were severe (Grade 3 or 4). Mood effects occurred in 24% of patients; 1.8% of these events were severe. Speech effects occurred in 14% of patients; 0.3% of these events were severe. Hallucinations occurred in 7% of patients; 0.6% of these events were severe. Mental status changes occurred in 2.1% of patients; 1.8% of these events were severe. Seizures occurred in 3% of patients, sometimes in conjunction with other neurologic findings. Sleep effects occurred in 10% of patients. The median time to first onset of any CNS effect was 1.2 months (1 day to 1.7 years). Overall, 1.5% of patients required permanent discontinuation of LORBRENA for a CNS effect; 9% 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 17% and Grade 3 or 4 elevations in triglycerides occurred in 17% of the 332 patients who received LORBRENA in Study B7461001. The median time to onset was 15 days for both hypercholesterolemia and hypertriglyceridemia. Approximately 7% of patients required temporary discontinuation and 3% of patients required dose reduction of LORBRENA for elevations in cholesterol and in triglycerides. Eighty percent of patients required initiation of lipid-lowering medications, with a median time to onset of start of such medications of 21 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 295 patients who received LORBRENA at a dose of 100 mg orally once daily in Study B7461001 and who had a baseline electrocardiography (ECG), 1% experienced AV block and 0.3% 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 1.5% of patients who received LORBRENA at any dose in Study B7461001, including Grade 3 or 4 ILD/pneumonitis in 1.2% of patients. One patient (0.3%) 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]*.

**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 295 patients in Study B7461001 who received 100 mg LORBRENA orally once daily, 18% of patients were aged 65 years or older. Although data are limited, no clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients.

**Hepatic Impairment**

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] with AST > ULN or total bilirubin >1 to 1.5 × ULN with any AST). The recommended dose of LORBRENA has not been established for patients with moderate or severe hepatic impairment *[see 5.2 Pharmacokinetic properties]*.

**Renal Impairment**

No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min estimated by Cockcroft-Gault). The recommended dose of LORBRENA has not been established for patients with severe renal impairment *[see 5.2 Pharmacokinetic properties]*.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Effect of Other Drugs on LORBRENA**

Effect of CYP3A Inducers

Concomitant use of LORBRENA with a strong CYP3A inducer decreased lorlatinib plasma concentrations, which may decrease the efficacy of LORBRENA. The effect of concomitant use of LORBRENA with a moderate CYP3A inducer on lorlatinib plasma concentrations has not been studied.

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. The risk of hepatotoxicity with concomitant use of LORBRENA and moderate CYP3A inducers that are also PXR agonists is unknown.

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. If concomitant use of moderate CYP3A inducers cannot be avoided, monitor ALT, AST, and bilirubin as recommended *[see 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 5.2 Pharmacokinetic properties]*.

Effect of Strong CYP3A Inhibitors

Concomitant use with a strong CYP3A inhibitor increased lorlatinib plasma concentrations*,* which may increase the incidence and severity of adverse reactions of LORBRENA. Avoid the concomitant use of LORBRENA with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce LORBRENA dose as recommended *[see 4.2 Posology and method of administration, 5.2Pharmacokinetic properties]*.

CYP3A Substrates

Concomitant use of LORBRENA decreases the concentration of CYP3A substrates *[see* *5.2 Pharmacokinetic properties]*, which may reduce the efficacy of these substrates. Avoid concomitant use of LORBRENA with CYP3A substrates, where 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.

**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).

* 1. **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 ]*

**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 data in Warnings and Precautions reflect exposure to LORBRENA in 332 patients with ALK‑positive or 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 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. 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 Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (96%).

The most common (≥20%) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea; the most common (≥20%) laboratory abnormalities 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 2 and 3 summarize common adverse reactions and laboratory abnormalities, respectively, in patients treated with LORBRENA in Study B7461001.

| **Table 2 Adverse Reactions Occurring in ≥10% of Patients in Study B7461001\*** | | |
| --- | --- | --- |
| **Adverse Reaction** | **LORBRENA**  **(N=295)** | |
| **All Grades**  **(%)** | **Grade 3 or 4**  **(%)** |
| Psychiatric  Mood effectsa | 23 | 1.7 |
| Nervous system  Peripheral neuropathyb  Cognitive effectsc  Headache  Dizziness  Speech effectsd  Sleep effectse | 47  27  18  16  12  10 | 2.7  2.0  0.7  0.7  0.3  0 |
| Respiratory  Dyspnea  Cough | 27  18 | 5.4  0 |
| Ocular  Vision disorderf | 15 | 0.3 |
| Gastrointestinal  Diarrhea  Nausea  Constipation  Vomiting | 22  18  15  12 | 0.7  0.7  0  1 |
| Musculoskeletal and connective tissue  Arthralgia  Myalgiag  Back pain  Pain in extremity | 23  17  13  13 | 0.7  0  0.7  0.3 |
| General  Edemah  Fatiguei  Weight gain  Pyrexia | 57  26  24  12 | 3.1  0.3  4.4  0.7 |
| Infections  Upper respiratory tract infectionj | 12 | 0 |
| Skin  Rashk | 14 | 0.3 |

\* Adverse reactions were graded using NCI CTCAE version 4.0.

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 hallucinations (7%).

|  |  |  |
| --- | --- | --- |
| **Table 3 Worsening Laboratory Values Occurring in ≥20% of Patients in Study B7461001\*** | | |
| **Laboratory Abnormality** | **LORBRENA** | |
| **All Grades**  **(%)** | **Grade 3 or 4**  **(%)** |
| Chemistry  Hypercholesterolemiaa  Hypertriglyceridemiaa  Hyperglycemiab  Increased ASTa  Hypoalbuminemiac  Increased ALTa  Increased lipased  Increased alkaline phosphatasea  Increased amylasee  Hypophosphatemiaa  Hyperkalemiab  Hypomagnesemiaa | 96  90  52  37  33  28  24  24  22  21  21  21 | 18  18  5  2.1  1.0  2.1  10  1.0  3.9  4.8  1.0  0 |
| Hematology  Anemiab  Thrombocytopeniab  Lymphopeniaa | 52  23  22 | 4.8  0.3  3.4 |
| \* Grades using NCI CTCAE version 4.0.  Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.  N=number of patients who had at least one on‑study assessment for the parameter of interest.  a N=292.  b N=293.  c N=291.  d N=290.  e N=284. | | |

**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 according to their local requirements.

To report any side effects:

|  |
| --- |
| **Saudi Arabia**  **National Pharmacovigilance Center ( NPC )**   * Fax: +966 11 205 7662 * Call NPC at 00966 11 2038222, Exts: 2317-2356-2340 * Call center :19999 * E-mail: [npc.drug@sfda.gov.sa](mailto:npc.drug@sfda.gov.sa)   Website: [www.sfda.gov.sa/npc](http://www.sfda.gov.sa/npc) |

**4.9 Overdose**

**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

Based on the data from Study B7461001, 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**

**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 non‑small cell lung cancer (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 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), 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 4). The major efficacy outcome measures were overall response rate (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 4. Additional efficacy outcome measures included duration of response (DOR), and intracranial DOR.

A total of 215 patients were enrolled across the subgroups in Table 4. The distribution of patients by type and extent of prior therapy is provided in Table 4. 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.

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| **Table 4 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 chemotherapya | 29 |
| Prior crizotinib and 1-2 lines of prior chemotherapya | 35 |
| Prior ALK inhibitor (not crizotinib) with or without prior chemotherapya | 28 |
| Two prior ALK inhibitors with or without prior chemotherapya | 75 |
| Three prior ALK inhibitors with or without prior chemotherapya | 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 5 and 6.

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| **Table 5 Efficacy Results in Study B7461001** | |
| **Efficacy Parameter** | **Overall**  **N=215** |
| **Overall response ratea** (95% CI)b  Complete response  Partial response | 48% (42, 55)  4%  44% |
| **Duration of response**  Median, monthsc (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 6. 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.

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| **Table 6 Intracranial Response Rate in Patients with Measurable Intracranial Lesions in Study B7461001** | |
| **Efficacy Parameter** | **Intracranial**  **N=89** |
| **Intracranial response ratea** (95% CI)b  Complete response  Partial response | 60% (49, 70)  21%  38% |
| **Duration of response**  Median, monthsc (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**

##### Steady-state lorlatinib maximum plasma concentration (Cmax) 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). At the recommended dosage, the mean (coefficient of variation [CV] %) Cmax was 577 ng/mL (42%) and the AUC0-24h was 5650 ng·h/mL (39%) in patients with cancer. Lorlatinib oral clearance increased at steady-state compared to single dose, indicating autoinduction.

##### Absorption

##### The median lorlatinib Tmax was 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 75.7%, 86.2%) after oral administration compared to intravenous administration.

##### Effect of Food

##### Administration of LORBRENA with 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) had no clinically meaningful effect on lorlatinib pharmacokinetics.

##### Distribution

##### In vitro, lorlatinib was 66% bound to plasma proteins at a concentration of 2.4 µM. The blood-to-plasma ratio was 0.99. The mean (CV%) steady state volume of distribution (Vss) was 305 L (28%) following a single intravenous dose.

##### 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

##### In vitro, 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 in a human [14C] mass balance study. 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 meaningful differences in lorlatinib pharmacokinetics were observed based on age (19 to 85 years), sex, race/ethnicity, body weight, mild to moderate renal impairment (CLcr 30 to 89 mL/min), mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1.5 × ULN and any AST), or metabolizer phenotypes for CYP3A5 and CYP2C19. The effect of moderate to severe hepatic impairment or severe renal impairment on lorlatinib pharmacokinetics is unknown [see Use in Specific Populations (8.6, 8.7)].

##### Drug Interaction Studies

##### Clinical Studies

##### Effect of CYP3A Inducers on Lorlatinib: Twelve healthy subjects received rifampin, a strong CYP3A inducer that also activates PXR, 600 mg once daily for 8 days (Days 1 to 8) and a single oral 100 mg dose of LORBRENA on Day 8. The coadministration of rifampin with LORBRENA reduced the mean lorlatinib AUCinf by 85% and Cmax 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). 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 [see 4.5 Interaction with other medical products and other forms of interactions].

##### Effect of Strong CYP3A Inhibitors on Lorlatinib: Itraconazole, a strong CYP3A inhibitor, increased AUCinf by 42% and increased Cmax by 24% of a single oral 100 mg dose of LORBRENA [see 4.5 Interaction with other medical products and other forms of interactions].

##### Effect of Lorlatinib on CYP3A Substrates: LORBRENA 150 mg orally once daily for 15 days decreased AUCinf by 64% and Cmax by 50% of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate) [see 4.5 Interaction with other medicinal products and other forms of interaction].

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

##### In Vitro Studies

##### Effect of Lorlatinib on CYP Enzymes: In vitro studies indicate that 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, and CYP2D6. M8 does not inhibit CYP3A.

##### M8 does not induce CYP1A2, CYP2B6, and CYP3A.

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

##### Effect of Lorlatinib on Transporters: Lorlatinib inhibits P glycoprotein (P gp), organic cation transporter (OCT)1, organic anion transporter (OAT)3, multidrug and toxin extrusion (MATE)1, and intestinal breast cancer resistance protein (BCRP). Lorlatinib does not inhibit organic anion transporting polypeptide (OATP)1B1, OATP1B3, OAT1, OCT2, MATE2K, and systemic BCRP. M8 does not inhibit P gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K.

**5.3 Preclinical safety data**

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**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**

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

**6.4 Special precautions for storage**

**Keep out of the sight and reach of children.**

* 1. **Nature and contents of container**

Tablets:

* 25 mg: 8 mm round, tan, immediate release, film-coated, debossed with “Pfizer” on one side and “25” and “LLN” on the other side
* 100 mg: 8.5 mm × 17 mm oval, lavender, immediate release, film-coated, debossed with “Pfizer” on one side and “LLN 100” on the other side

**6.6 Special precautions for disposal and other handling**

**Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.**

**PATIENT COUNSELING INFORMATION**

# PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers

Inform patients of the potential risk of hepatoxicity with the concomitant use of strong CYP3A inducers.

Advise patients to inform their healthcare providers of all medications they are taking, including prescription medicines, over-the-counter drugs, vitamins, and herbal products (e.g., St. John's wort) *[see 4.4 Special warnings and precautions for use ]*.

Central Nervous System (CNS) Effects

Advise patients to notify their healthcare provider if they experience new or worsening CNS symptoms *[see 4.4 Special warnings and precautions for use].*

Hyperlipidemia

Inform patients that serum cholesterol and triglycerides will be monitored during treatment. Advise patients that initiation or an increase in the dose of lipid-lowering agents may be required *[see 4.4 Special warnings and precautions for use]*.

Atrioventricular (AV) Block

Inform patients of the risks of AV block. Advise patients to contact their healthcare provider immediately to report new or worsening cardiac symptoms *[see 4.4 Special warnings and precautions for use]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risks of severe ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see 4.4 Special warnings and precautions for use]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see 4.4 Special warnings and precautions for use, 4.6 Fertility, Pregnancy and lactation]*.

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with LORBRENA and for at least 6 months after the final dose *[see 4.6 Fertility, Pregnancy and lactation]*.

Advise male patients 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 4.6 Fertility, Pregnancy and lactation, 5.3 Preclinical safety data]*.

Lactation

Advise women not to breastfeed during treatment with LORBRENA and for 7 days after the final dose *[see 4.6 Fertility, Pregnancy and lactation]*.

Infertility

Advise males of reproductive potential that LORBRENA may transiently impair fertility *[see 4.6 Fertility, Pregnancy and lactation, 5.3 Preclinical safety data]*.

**7. FURTHER INFORMATION**

**MARKETING AUTHORISATION HOLDER**

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

**MANUFACUTRED BY**

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

**PACKED & RELEASED BY**

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

**9. DATE OF REVISION OF THE TEXT**

November 2018

**THIS IS A MEDICAMENT**

* Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
* Follow strictly the doctor’s prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
* The doctor and the Pharmacist are experts in medicines, their benefits and risks.
* Do not by yourself interrupt the period of treatment prescribed.
* Do not repeat the same prescription without consulting your doctor.

**Keep all medicaments out of reach and sight of children**

**Council of Arab Health Ministers**

**Union of Arabic Pharmacists**