LORVIQUA®
(Lorlatinib)

1 INDICATIONS AND USAGE

LORVIQUA 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of LORVIQUA is 100 mg orally once daily, with or without food, until disease progression or unacceptable toxicity *[see Clinical Pharmacology (10.3)]*.

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

Take LORVIQUA 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 LORVIQUA but continue with the next scheduled dose.

2.2 Dosage Modifications for Adverse Reactions

The recommended dose reductions are:

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

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

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

Table 1 Recommended LORVIQUA Dosage Modifications for Adverse Reactions

Adverse Reaction[a]	**Dosage Modifications**
Central Nervous System Effects *[see Warnings and Precautions (5.2)]*	
Grade 1	Continue at the same dose or withhold the dose until recovery to baseline. Resume LORVIQUA at the same dose or at a reduced dose.
Grade 2 OR Grade 3	Withhold dose until Grade 0 or 1. Resume LORVIQUA at a reduced dose.
Grade 4	Permanently discontinue LORVIQUA.
Hyperlipidemia *[see Warnings and Precautions (5.3)]*	
Grade 4 hypercholesterolemia OR Grade 4 hypertriglyceridemia	Withhold LORVIQUA until recovery of hypercholesterolemia and/or hypertriglyceridemia to less than or equal to Grade 2. Resume LORVIQUA at the same dose. If severe hypercholesterolemia and/or hypertriglyceridemia recurs, resume LORVIQUA at a reduced dose.
Atrioventricular (AV) Block *[see Warnings and Precautions (5.4)]*	
Second-degree AV block	Withhold LORVIQUA until PR interval is less than 200 ms. Resume LORVIQUA at a reduced dose.
First occurrence of complete AV block	Withhold LORVIQUA until • pacemaker placed OR • PR interval less than 200 ms. If a pacemaker is placed, resume LORVIQUA at the same dose. If no pacemaker is placed, resume LORVIQUA at a reduced dose.
Recurrent complete AV block	Place pacemaker or permanently discontinue LORVIQUA.
Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.5)]*	
Any Grade treatment–related ILD/Pneumonitis	Permanently discontinue LORVIQUA.

Table 1 Recommended LORVIQUA Dosage Modifications for Adverse Reactions

Adverse Reaction[a]	Dosage Modifications
Other Adverse Reactions	
Grade 1 OR Grade 2	Continue LORVIQUA at same dose or reduced dose.
Grade 3 OR Grade 4	Withhold LORVIQUA until symptoms resolve to less than or equal to Grade 2 or baseline. Resume LORVIQUA at reduced dose.

Abbreviation: AV=atrioventricular.

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

2.3 Concomitant Use of Strong or Moderate CYP3A Inducers

LORVIQUA 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 LORVIQUA. Avoid concomitant use of LORVIQUA with moderate CYP3A inducers *[see Warnings and Precautions (5.1), Clinical Pharmacology (10.3)]*.

2.4 Dosage Modification for Strong CYP3A Inhibitors

Avoid concomitant use of LORVIQUA with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor cannot be avoided, reduce the starting dose of LORVIQUA 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 LORVIQUA dose to 50 mg orally once daily.

If concomitant use of a strong CYP3A inhibitor is discontinued, increase the LORVIQUA dose (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor *[see Clinical Pharmacology (10.3)]*.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

LORVIQUA is contraindicated in patients taking strong CYP3A inducers, due to the potential for serious hepatotoxicity *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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 LORVIQUA 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.

LORVIQUA 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 LORVIQUA.

Avoid concomitant use of LORVIQUA with moderate CYP3A inducers. If concomitant use of moderate CYP3A inducers cannot be avoided, monitor AST, ALT, and bilirubin 48 hours after initiating LORVIQUA and at least 3 times during the first week after initiating LORVIQUA.

Depending upon the relative importance of each drug, discontinue LORVIQUA or the CYP3A inducer for persistent Grade 2 or higher hepatotoxicity *[see Clinical Pharmacology (10.3)]*.

5.2 Central Nervous System Effects

A broad spectrum of central nervous system (CNS) effects can occur in patients receiving LORVIQUA. 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 LORVIQUA *[see Adverse Reactions (6.1)]*. Cognitive effects occurred in 29% of the 332 patients who received LORVIQUA 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 LORVIQUA 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 LORVIQUA based on severity *[see Dosage and Administration (2.2)]*.

5.3 Hyperlipidemia

Increases in serum cholesterol and triglycerides can occur in patients receiving LORVIQUA *[see Adverse Reactions (6.1)]*. 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 LORVIQUA 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 LORVIQUA 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 LORVIQUA, 1 and 2 months after initiating LORVIQUA, and periodically thereafter. Withhold and resume at the same dose for the first occurrence; resume at the same or a reduced dose of LORVIQUA for recurrence based on severity *[see Dosage and Administration (2.2)]*.

5.4 Atrioventricular Block

PR interval prolongation and atrioventricular (AV) block can occur in patients receiving LORVIQUA *[see Adverse Reactions (6.1), Clinical Pharmacology (10.2)]*. In 295 patients who received LORVIQUA 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 LORVIQUA 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 Dosage and Administration (2.2)]*.

5.5 Interstitial Lung Disease/Pneumonitis

Severe or life-threatening pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis can occur with LORVIQUA. ILD/pneumonitis occurred in 1.5% of patients who received LORVIQUA at any dose in Study B7461001, including Grade 3 or 4 ILD/pneumonitis in 1.2% of patients. One patient (0.3%) discontinued LORVIQUA 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 LORVIQUA in patients with suspected ILD/pneumonitis. Permanently discontinue LORVIQUA for treatment-related ILD/pneumonitis of any severity *[see Dosage and Administration (2.2)]*.

5.6 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, LORVIQUA 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 LORVIQUA can render hormonal contraceptives ineffective, during treatment with LORVIQUA 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 LORVIQUA and for 3 months after the final dose *[see Drug Interactions (7.2), Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (11.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers *[see Warnings and Precautions (5.1)]*
- Central Nervous System Effects *[see Warnings and Precautions (5.2)]*
- Hyperlipidemia *[see Warnings and Precautions (5.3)]*
- Atrioventricular Block *[see Warnings and Precautions (5.4)]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.5)]*

6.1 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 LORVIQUA 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 LORVIQUA at doses ranging from 10 mg to 200 mg daily in single or divided doses.

The data described below reflect exposure to LORVIQUA in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORVIQUA 100 mg orally once daily in Study B7461001. The median duration of exposure to LORVIQUA was 12.5 months (1 day to 35 months) and 52% received LORVIQUA 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. Of the worsening laboratory values occurring in ≥20% of patients, the most common 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 LORVIQUA 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 LORVIQUA in Study B7461001.

Table 2 Adverse Reactions Occurring in ≥10% of Patients in Study B7461001*

Adverse Reaction	**LORVIQUA (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	2.0
Headache	18	0.7
Dizziness	16	0.7
Speech effects[d]	12	0.3
Sleep effects[e]	10	0
Respiratory		
Dyspnea	27	5.4
Cough	18	0
Ocular		
Vision disorder[f]	15	0.3
Gastrointestinal		
Diarrhea	22	0.7

Table 2 Adverse Reactions Occurring in ≥10% of Patients in Study B7461001*

Adverse Reaction	LORVIQUA (N=295)	
	All Grades (%)	Grade 3 or 4 (%)
Nausea	18	0.7
Constipation	15	0
Vomiting	12	1
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 4.0.

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	LORVIQUA	
	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	1.0
Increased ALT[a]	28	2.1
Increased lipase[d]	24	10
Increased alkaline phosphatase[a]	24	1.0
Increased amylase[e]	22	3.9
Hypophosphatemia[a]	21	4.8
Hyperkalemia[b]	21	1.0
Hypomagnesemia[a]	21	0
Hematology		
Anemia[b]	52	4.8
Thrombocytopenia[b]	23	0.3
Lymphopenia[a]	22	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.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on LORVIQUA

Effect of CYP3A Inducers

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

Severe hepatotoxicity occurred in healthy subjects receiving LORVIQUA with rifampin, a strong CYP3A inducer. In 12 healthy subjects receiving a single 100 mg dose of LORVIQUA 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 LORVIQUA and rifampin, which are both PXR agonists. The risk of hepatotoxicity with concomitant use of LORVIQUA and moderate CYP3A inducers that are also PXR agonists is unknown.

LORVIQUA 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 LORVIQUA.

Avoid concomitant use of LORVIQUA with moderate CYP3A inducers. If concomitant use of moderate CYP3A inducers cannot be avoided, monitor ALT, AST, and bilirubin as recommended *[see Dosage and Administration (2.3), Warnings and Precautions (5.1), Clinical Pharmacology (10.3)]*.

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 LORVIQUA. Avoid the concomitant use of LORVIQUA with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce LORVIQUA dose as recommended *[see Dosage and Administration (2.4), Clinical Pharmacology (10.3)]*.

7.2 Effect of LORVIQUA on Other Drugs

CYP3A Substrates
Concomitant use of LORVIQUA decreases the concentration of CYP3A substrates *[see Clinical Pharmacology (10.3)]*, which may reduce the efficacy of these substrates. LORVIQUA is considered a moderate CYP3A inducer. Avoid concomitant use of LORVIQUA with 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.

P-glycoprotein (P-gp) Substrates
Concomitant use of LORVIQUA decreases the concentration of P-gp substrates *[see Clinical Pharmacology (10.3)]*, which may reduce the efficacy of these substrates. LORVIQUA is considered a moderate P-gp inducer. Avoid concomitant use of LORVIQUA with 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (10.1)]*, LORVIQUA can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on LORVIQUA 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.

8.2 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 LORVIQUA and for 7 days after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating LORVIQUA *[see Use in Specific Populations (8.1)]*.

Contraception
LORVIQUA can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females
Advise female patients of reproductive potential to use effective non-hormonal contraception during treatment with LORVIQUA and for at least 6 months after the final dose. Advise females of reproductive potential to use a non-hormonal method of contraception, because LORVIQUA can render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with LORVIQUA and for at least 3 months after the final dose *[see Nonclinical Toxicology (11.1)]*.

Infertility

Males
Based on findings from animal studies, LORVIQUA may transiently impair male fertility *[see Nonclinical Toxicology (11.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 295 patients in Study B7461001 who received 100 mg LORVIQUA 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.

8.6 Hepatic Impairment

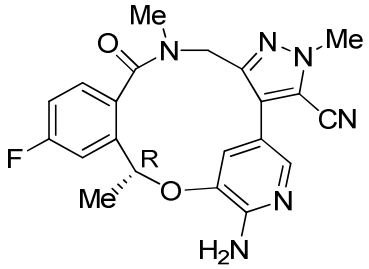
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] with AST > ULN or total bilirubin >1 to 1.5 × ULN with any AST). The recommended dose of LORVIQUA has not been established for patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (10.3)]*.

8.7 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 LORVIQUA has not been established for patients with severe renal impairment *[see Clinical Pharmacology (10.3)]*.

9 DESCRIPTION

LORVIQUA (lorlatinib) is a kinase inhibitor for oral administration. The molecular formula is $C_{21}H_{19}FN_6O_2$ (anhydrous form) and the molecular weight is 406.41 Daltons. The chemical name is (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3-*h*][2,5,11] benzoxadiazacyclotetradecine-3-carbonitrile. 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.

LORVIQUA 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 4000/polyethylene glycol (PEG) 3350, triacetin, titanium dioxide, ferrosoferric oxide/black iron oxide, and iron oxide red.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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 LORVIQUA 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 LORVIQUA. The prolongation of PR interval occurred in a concentration-dependent manner. Atrioventricular block occurred in 1% of patients.

In 275 patients who received LORVIQUA 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.

10.3 Pharmacokinetics

Steady-state lorlatinib maximum plasma concentration (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). At the recommended dosage, the mean (coefficient of variation [CV] %) C_{max} was 577 ng/mL (42%) and the $AUC_{0\text{-}24h}$ 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 T_{max} 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 LORVIQUA 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 (V_{ss}) was 305 L (28%) following a single intravenous dose.

Elimination
The mean plasma half-life ($t_{½}$) of lorlatinib was 24 hours (40%) after a single oral 100 mg dose of LORVIQUA. 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 [^{14}C] 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 LORVIQUA on Day 8. The coadministration of rifampin with LORVIQUA reduced the mean lorlatinib AUC_{inf} 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). 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 Drug Interactions (7.1)]*.

Effect of Strong CYP3A Inhibitors on Lorlatinib: Itraconazole, a strong CYP3A inhibitor, increased AUC_{inf} by 42% and increased C_{max} by 24% of a single oral 100 mg dose of LORVIQUA *[see Drug Interactions (7.1)]*.

Effect of Lorlatinib on CYP3A Substrates: LORVIQUA 150 mg orally once daily for 15 days decreased AUC_{inf} by 64% and C_{max} by 50% of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate) *[see Drug Interactions (7.2)]*.

Effect of Lorlatinib on CYP2B6 Substrates: LORVIQUA 100 mg orally once daily for 15 days decreased AUC_{inf} by 25% and C_{max} by 27% of a single oral 100 mg dose of bupropion (a sensitive CYP2B6 substrate).

Effect of Lorlatinib on CYP2C9 Substrates: LORVIQUA 100 mg orally once daily for 15 days decreased AUC_{inf} by 43% and C_{max} by 15% of a single oral 100 mg dose of tolbutamide (a sensitive CYP2C9 substrate).

Effect of Lorlatinib on UGT1A Substrates: LORVIQUA 100 mg orally once daily for 15 days decreased AUC_{inf} by 45% and C_{max} by 28% of a single oral 100 mg dose of acetaminophen (a UGT1A substrate).

Effect of Lorlatinib on P-gp Substrates: LORVIQUA 100 mg orally once daily for 15 days decreased AUC_{inf} by 67% and C_{max} by 63% of a single oral 60 mg dose of fexofenadine (a P-gp substrate) *[see Drug Interactions (7.2)],* suggesting induction of P-gp activity.

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: In vitro studies indicate that 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. *In vitro* studies also indicate that lorlatinib inhibits 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.

11 NONCLINICAL TOXICOLOGY

11.1 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.

11.2 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.

12 CLINICAL STUDIES

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

The efficacy of LORVIQUA 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 LORVIQUA 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.

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 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 5 and 6.

Table 5 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 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 LORVIQUA.

Table 6 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 LORVIQUA 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

13 STORAGE AND HANDLING

Please refer to the outer packaging for the recommended storage condition.

14 PATIENT COUNSELING 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 Warnings and Precautions (5.1)]*.

Central Nervous System (CNS) Effects
Advise patients to notify their healthcare provider if they experience new or worsening CNS symptoms *[see Warnings and Precautions (5.2)]*.

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 Warnings and Precautions (5.3)]*.

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 Warnings and Precautions (5.4)]*.

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 Warnings and Precautions (5.5)]*.

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 Warnings and Precautions (5.6), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with LORVIQUA and for at least 6 months after the final dose *[see Use in Specific Populations (8.3)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LORVIQUA and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (11.1)]*.

Lactation

Advise women not to breastfeed during treatment with LORVIQUA and for 7 days after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that LORVIQUA may transiently impair fertility *[see Use in Specific Populations (8.3), Nonclinical Toxicology (11.1)]*.

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