LORVIQUA

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LORVIQUA FILM-COATED TABLET
Lorlatinib

1. NAME OF THE MEDICINAL PRODUCT

LORVIQUA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25 mg film-coated tablet contains 25 mg of lorlatinib.

Each 100 mg film-coated tablet contains 100 mg of lorlatinib.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LORVIQUA is indicated for the first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

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.

4.2 Posology and method of administration

ALK testing

Detection of ALK-positive NSCLC is necessary for selection of patients for treatment with lorlatinib because these are the only patients for whom benefit has been shown. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised. Improper assay performance can lead to unreliable test results.

Recommended dosing

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

LORVIQUA may be taken with or without food (see Section 5.2).

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

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

Dose modifications

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

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

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

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

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	**LORVIQUA Dosing**
Hypercholesterolaemia or Hypertriglyceridaemia	
Mild hypercholesterolaemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L)	Introduce or modify lipid-lowering therapy[a] in accordance with respective prescribing information; continue LORVIQUA at same dose.

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	**LORVIQUA Dosing**
OR Moderate hypercholesterolaemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L)	
Mild hypertriglyceridaemia (triglycerides between 150 and 300 mg/dL or 1.71 and 3.42 mmol/L) OR Moderate hypertriglyceridaemia (triglycerides between 301 and 500 mg/dL or 3.43 and 5.7 mmol/L)	
Severe hypercholesterolaemia (cholesterol between 401 and 500 mg/dL or between 10.35 and 12.92 mmol/L) OR Severe hypertriglyceridaemia (triglycerides between 501 and 1000 mg/dL or 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy;[a] if currently on lipid-lowering therapy, increase the dose of this therapy[a] in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue LORVIQUA at the same dose without interruption.
Life-threatening hypercholesterolaemia (cholesterol over 500 mg/dL or over 12.92 mmol/L) OR Life-threatening hypertriglyceridaemia (triglycerides over 1000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[a] or increase the dose of this therapy[a] in accordance with respective prescribing information or change to a new lipid-lowering therapy. Withhold LORVIQUA until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to moderate or mild severity grade. Re-challenge at same LORVIQUA dose while maximizing lipid-lowering therapy[a] in accordance with respective prescribing information. If severe hypercholesterolaemia and/or hypertriglyceridaemia recur(s) despite maximal lipid-lowering therapy[a] in accordance with respective prescribing information, reduce LORVIQUA by 1 dose level.
Central nervous system (CNS) effects[b,c]	
Grade 1: Mild	Continue at the same dose or withhold dose until recovery to baseline. Then resume

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	**LORVIQUA Dosing**
	LORVIQUA at the same dose or reduce by 1 dose level.
Grade 2: Moderate OR Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume LORVIQUA at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue LORVIQUA.
Interstitial lung disease/Pneumonitis	
Grade 1: Mild OR Grade 2: Moderate	Withhold LORVIQUA until symptoms have returned to baseline and consider initiating corticosteroids. Resume LORVIQUA at 1 reduced dose level. Permanently discontinue LORVIQUA if ILD/pneumonitis recurs or fails to recover after 6 weeks of LORVIQUA hold and steroid treatment.
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue LORVIQUA.
Lipase/Amylase increase	
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Withhold LORVIQUA until lipase or amylase returns to baseline. Then resume LORVIQUA at 1 reduced dose level.
PR interval prolongation/Atrioventricular (AV) block	
First-degree AV block: Asymptomatic	Continue LORVIQUA at the same dose without interruption. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to heart block closely.
First-degree AV block: Symptomatic	Withhold LORVIQUA. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If symptoms resolve, resume LORVIQUA at 1 reduced dose level.
Second-degree AV block:	Withhold LORVIQUA. Consider effects of

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	**LORVIQUA Dosing**
Asymptomatic	concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to heart block closely. If subsequent ECG does not show second-degree AV block, resume LORVIQUA at 1 reduced dose level.
Second-degree AV block: Symptomatic	Withhold LORVIQUA. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic AV block persists. If symptoms and the second-degree AV block resolve or if patients revert to asymptomatic first-degree AV block, resume LORVIQUA at 1 reduced dose level.
Complete AV block	Withhold LORVIQUA. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Pacemaker placement may be indicated for severe symptoms associated with AV block. If AV block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, resume LORVIQUA at full dose. If no pacemaker placed, resume LORVIQUA at 1 reduced dose level only when symptoms resolve and PR interval is less than 200 msec.
Hypertension	
Grade 3 (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg; medical intervention indicated; more than one antihypertensive drug, or more intensive therapy than previously used indicated)	Withhold LORVIQUA until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume LORVIQUA at the same dose. If Grade 3 hypertension recurs, withhold LORVIQUA until recovery to Grade 1 or less, and resume at a reduced dose. If adequate hypertension control cannot be achieved with optimal medical management, permanently discontinue LORVIQUA.

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	**LORVIQUA Dosing**
Grade 4 (life-threatening consequences, urgent intervention indicated)	Withhold LORVIQUA until recovery to Grade 1 or less, and resume at a reduced dose or permanently discontinue LORVIQUA. If Grade 4 hypertension recurs, permanently discontinue LORVIQUA.
Hyperglycaemia	
Grade 3 OR Grade 4 (persistent hyperglycaemia greater than 250 mg/dL despite optimal anti-hyperglycaemic therapy)	Withhold LORVIQUA until hyperglycaemia is adequately controlled, then resume LORVIQUA at the next lower dosage. If adequate hyperglycaemic control cannot be achieved with optimal medical management, permanently discontinue LORVIQUA.
Other adverse drug reactions[c]	
Grade 1 OR Grade 2	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3	Withhold LORVIQUA until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume LORVIQUA at 1 reduced dose level.

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

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

[b] Examples of CNS effects comprise psychotic effects and changes in cognition, mood, mental status, or speech (see Sections 4.4 and 4.8).

[c] Grade categories are based on CTCAE classifications.

Strong cytochrome P-450 (CYP)3A inhibitors

Concurrent use of LORVIQUA with strong CYP3A inhibitors may increase lorlatinib plasma concentrations. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered (see Sections 4.5 and 5.2). If a strong CYP3A inhibitor must be administered concomitantly, the starting LORVIQUA dose of 100 mg once daily should be reduced to once daily 75 mg dose. If concurrent use of a strong CYP3A inhibitor is discontinued, LORVIQUA should be resumed at the dose used prior to the initiation of the strong CYP3A inhibitor and after a washout period of 3 to 5 half-lives of the strong CYP3A inhibitor.

Hepatic impairment

No dose adjustments are recommended for patients with mild or moderate hepatic impairment. A reduced starting dose of LORVIQUA is recommended in patients with severe

hepatic impairment (Child-Pugh C) from 100 mg to 50 mg orally once daily (see Section 5.2).

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment [absolute estimated glomerular filtration rate (eGFR): ≥30 mL/min]. A reduced dose of LORVIQUA is recommended in patients with severe renal impairment (absolute eGFR <30 mL/min), e.g., a starting dose of 75 mg taken orally once daily (see Section 5.2).

Elderly (≥65 years)

The limited data on the safety and efficacy of lorlatinib in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see Section 5.2).

Paediatric patients

The safety and efficacy of lorlatinib in paediatric patients has not been established.

4.3 Contraindications

Concomitant use of strong CYP3A inducers with lorlatinib is contraindicated due to the potential for serious hepatotoxicity (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] elevations) (see Sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Hyperlipidaemia

The use of lorlatinib has been associated with increases in serum cholesterol and triglycerides (see Section 4.8). Serum cholesterol and triglycerides should be monitored before initiation of lorlatinib; 2, 4, and 8 weeks after initiating lorlatinib; and periodically thereafter. Initiation, or increase in the dose, of lipid-lowering agents is required (see Section 4.2).

Central nervous system effects

Central nervous system (CNS) effects have been observed in patients receiving lorlatinib including seizures, psychotic effects, changes in cognitive function, mood (including suicidal ideation), mental status, sleep, and speech (see Section 4.8). Dose modification or discontinuation may be required for those patients who develop CNS effects (see Section 4.2).

Atrioventricular block

PR interval prolongation and atrioventricular (AV) block events have been reported in patients receiving LORVIQUA. Monitor electrocardiogram (ECG) prior to initiating lorlatinib and monthly thereafter, particularly in patients with predisposing conditions to the occurrence of clinically significant cardiac events. Dose modification may be required for those patients who develop AV block (see Section 4.2).

Lipase and amylase increase

Elevations of lipase and/or amylase have occurred in patients receiving lorlatinib (see Section 4.8). Median time of occurrence of increase in serum lipase and amylase is 70 days (range: 7 to 696 days) and 41 days (range: 7 to 489 days), respectively. Risk of pancreatitis should be considered in patients receiving lorlatinib due to concomitant hypertriglyceridaemia and/or a potential intrinsic mechanism. Patients should be monitored for lipase and amylase elevations prior to the start of lorlatinib treatment and regularly thereafter as clinically indicated (see Section 4.2).

Interstitial lung disease/pneumonitis

Severe or life threatening pulmonary adverse drug reactions consistent with ILD/pneumonitis have occurred with lorlatinib (see Section 4.8). Any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough and fever) should be promptly evaluated for ILD/pneumonitis. Lorlatinib should be withheld and/or permanently discontinued based on severity (see Section 4.2).

Hypertension

Hypertension has been reported in patients receiving lorlatinib (see Section 4.8). Blood pressure should be controlled prior to initiation of lorlatinib. Blood pressure should be monitored after 2 weeks and at least monthly thereafter during treatment with lorlatinib. Lorlatinib should be withheld and resumed at a reduced dose or permanently discontinued based on severity (see Section 4.2).

Hyperglycaemia

Hyperglycaemia has occurred in patients receiving lorlatinib (see Section 4.8). Fasting serum glucose should be assessed prior to initiation of lorlatinib and monitored periodically thereafter. Lorlatinib should be withheld and resumed at a reduced dose or permanently discontinued based on severity (see Section 4.2).

Drug-drug interactions

In a study conducted in healthy volunteers, the concomitant use of lorlatinib and rifampin, a strong CYP3A inducer was associated with increases of ALT and AST with no increase of total bilirubin and alkaline phosphatase (see Section 4.5). Concomitant use of any strong CYP3A inducer is contraindicated (see Sections 4.3 and 4.5). Any strong CYP3A inducers have to be discontinued for at least 3 plasma half-lives of the strong CYP3A inducer before lorlatinib treatment is started. No clinically meaningful changes in liver function tests were seen in healthy subjects after receiving a combination of lorlatinib with the moderate CYP3A inducer modafinil (see Section 4.5).

Fertility and pregnancy

Based on animal data and mechanism of action, there is a risk of fetal harm if exposed to LORVIQUA (see Sections 5.1 and 5.3). Women of childbearing potential should be advised to avoid becoming pregnant while receiving LORVIQUA. A highly effective non-hormonal method of contraception is required for female patients during treatment with LORVIQUA,

because lorlatinib can render hormonal contraceptives ineffective (see Sections 4.5 and 4.6). If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 21 days after completing therapy.

During treatment with LORVIQUA and for at least 97 days after the final dose, male patients with female partners of reproductive potential must use effective contraception, including a condom, and male patients with pregnant partners must use condoms (see Section 4.6). Male fertility may be compromised during treatment with lorlatinib (see Section 5.3). Men should seek advice on effective fertility preservation before treatment.

4.5 Interaction with other medicinal products and other forms of interaction

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

CYP3A inhibitors

Itraconazole, a strong inhibitor of CYP3A, administered at a dose of 200 mg once daily for 5 days, increased the mean area under the curve (AUC) by 42% and C_{max} by 24% of a single 100 mg oral dose of lorlatinib in healthy volunteers. Concomitant administration of lorlatinib with strong CYP3A inhibitors (e.g., boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, telaprevir, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either danoprevir, elvitegravir, indinavir, lopinavir, saquinavir, or tipranavir) may increase lorlatinib plasma concentrations. Grapefruit products may also increase lorlatinib plasma concentrations. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered. If a strong CYP3A inhibitor must be concomitantly administered, a dose reduction of lorlatinib is recommended (see Section 4.2).

CYP3A inducers

Rifampin, a strong inducer of CYP3A, administered at a dose of 600 mg once daily for 9 days, reduced the mean lorlatinib AUC by 85% and C_{max} by 76% of a single 100 mg dose of lorlatinib in healthy volunteers; increases in liver function tests (AST and ALT) were also observed. Concomitant administration of lorlatinib with strong CYP3A inducers (e.g., rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St. John's wort) may decrease lorlatinib plasma concentrations. The use of a strong CYP3A inducer with lorlatinib is contraindicated (see Sections 4.3 and 4.4). Any strong CYP3A inducers have to be discontinued for at least 3 plasma half-lives of the strong CYP3A inducer before lorlatinib treatment is started. No clinically meaningful changes in liver function test results were seen after administration of the combination of a single 100 mg oral dose of lorlatinib with the moderate CYP3A inducer, modafinil (400 mg once daily for 19 days) in healthy volunteers. Concomitant use of modafinil did not have a clinically meaningful effect on lorlatinib pharmacokinetics.

Proton-pump inhibitors, H_2-receptor antagonists, or locally acting antacids

The proton-pump inhibitor rabeprazole had a minimal effect on lorlatinib plasma exposure (90% confidence interval [CI] for the AUC_{inf} ratio, expressed as a percentage: 97.6%, 104.3%). No dose adjustment is required when lorlatinib is taken with proton-pump inhibitors, H_2-receptor antagonists, or locally acting-antacids.

Drugs whose plasma concentrations may be altered by lorlatinib

CYP3A substrates

Lorlatinib has a net induction effect on CYP3A both *in vitro* and *in vivo*. Lorlatinib 150 mg orally once daily for 15 days decreased AUC_{inf} by 64% and C_{max} by 50% of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate). Thus, concurrent administration of lorlatinib with CYP3A substrates with narrow therapeutic indices, including but not limited to hormonal contraceptives, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, should be avoided since the concentration of these drugs may be reduced by lorlatinib.

In vitro studies of other CYP inhibition and induction

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

In vitro studies indicated that lorlatinib is an inhibitor of CYP2C9 and that it activates the human pregnane-X-receptor (PXR), with the net effect *in vivo* being weak CYP2C9 induction. *In vitro* studies also indicated that lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A, with the net effect *in vivo* being induction. *In vitro* studies also indicated that lorlatinib is an inducer of CYP2B6 and activates the human constitutive androstane receptor (CAR) and *in vivo* lorlatinib is a weak inducer of CYP2B6. *In vitro*, lorlatinib has a low potential to cause drug-drug interactions by induction of CYP1A2.

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

In vitro studies of UDP-glucuronosyltransferase (UGT) inhibition

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

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

In vitro studies with drug transporters

In vitro studies indicated that clinical drug-drug interactions as a result of lorlatinib-mediated inhibition of breast cancer resistance protein (BCRP, systemically), multidrug and toxin extrusion protein (MATE)2K, organic anion transporter (OAT)1, and organic cation transporter (OCT)2 are unlikely. *In vitro* studies indicated that lorlatinib is an inhibitor of P-glycoprotein (P-gp) and that it activates PXR, with the net effect *in vivo* being moderate induction. Lorlatinib may have the potential to inhibit BCRP (GI tract), OATP1B1, OATP1B3, OCT1, MATE1, and OAT3 at clinically relevant concentrations.

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

In vivo studies with drug transporters

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females and males

Women of childbearing potential should be advised to avoid becoming pregnant while receiving LORVIQUA. A highly effective nonhormonal method of contraception is required for female patients during treatment with LORVIQUA, because lorlatinib can render hormonal contraceptives ineffective (see Sections 4.4 and 4.5). If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 21 days after completing therapy.

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

Pregnancy

Studies in animals have shown embryo-fetal toxicity (see Section 5.3). There are no data in pregnant women using LORVIQUA. LORVIQUA may cause fetal harm when administered to a pregnant woman.

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

Breastfeeding

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

LORVIQUA should not be used during breastfeeding. Breastfeeding should be discontinued during treatment with LORVIQUA and for 7 days after the last dose.

Fertility

Based on nonclinical safety findings, male fertility may be compromised during treatment with LORVIQUA (see Section 5.3). It is not known whether LORVIQUA affects female fertility. Men should seek advice on effective fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The data described below reflect exposure to LORVIQUA in 547 adult patients with ALK-positive or c-ros oncogene 1 (ROS1)-positive metastatic NSCLC who received LORVIQUA 100 mg orally once daily in single-arm Study B7461001, in randomised, open-label, active-controlled Phase 3 Study B7461006 or in single-arm, multicenter Phase 4 Study B7461027.

The median duration of treatment was 17.38 months (range: 5.65 day to 62.55 months), the median age was 56 years (range: 19 to 90 years), and 26% of patients were older than 65 years. A total of 55% of patients were female, 53% of patients were White, 36% of patients were Asian, and 1% were Black.

The most frequently reported adverse drug reactions were hypercholesterolaemia (79%), hypertriglyceridaemia (67.5%), oedema (55.4%), peripheral neuropathy (44.2%), weight increased (29.8%), cognitive effects (27.4%), fatigue (30.7%), arthralgia (27.8%), diarrhoea (22.7%), and mood effects (21.4%).

Serious adverse drug reactions were reported in 9.1% of patients receiving lorlatinib. The most frequent serious adverse drug reactions were cognitive effects and pneumonitis.

Dose reductions due to adverse drug reactions occurred in 20.1% of patients receiving lorlatinib. The most common adverse drug reactions that led to dose reductions were oedema, cognitive effects, and peripheral neuropathy. Permanent treatment discontinuation associated with adverse drug reactions occurred in 4.0% of patients receiving lorlatinib. The most frequent adverse drug reactions that led to a permanent discontinuation were cognitive effects, peripheral neuropathy, psychotic effects, and pneumonitis.

Table 2 presents adverse drug reactions for lorlatinib within each system organ class (SOC) by decreasing medical seriousness.

Table 2. Adverse Drug Reactions

System Organ Class	Adverse Drug Reaction
Metabolism and nutrition disorders	Hypercholesterolaemia[a] Hypertriglyceridaemia[b] Hyperglycaemia
Psychiatric disorders	Mood effects[c] Psychotic effects[d] Mental status changes
Nervous system disorders	Cognitive effects[e] Peripheral neuropathy[f] Speech effects[g] Sleep effects[h] Seizures
Eye disorders	Vision disorder[i]
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Pneumonitis[j]
Gastrointestinal disorders	Diarrhoea Constipation
Musculoskeletal and connective tissue disorders	Arthralgia
General disorders and administration site conditions	Oedema[k] Fatigue[l]
Investigations	Weight increased Lipase increased Amylase increased

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in the table above. Terms actually reported in the studies up to the data cut-off date (B7461001: 10Jul2023; B7461006: 29May2024; B7461027: 29May2024) and contributing to the relevant adverse drug reaction are indicated in parentheses, as listed below.

[a] Hypercholesterolaemia (including blood cholesterol increased, hypercholesterolaemia).

[b] Hypertriglyceridaemia (including blood triglycerides increased, hypertriglyceridaemia).

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

[d] Psychotic effects (including delusion, hallucination, hallucination auditory, hallucination visual, schizophreniform disorder).

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

[f] Peripheral neuropathy (including burning sensation, dysaesthesia, formication, gait disturbance, hypoaesthesia, motor dysfunction, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, sensory disturbance).

[g] Speech effects (including dysarthria, slow speech, speech disorder).

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

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

[j] Pneumonitis (including interstitial lung disease, lung opacity, pneumonitis).

[k] Oedema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).

[l] Fatigue (including asthenia, fatigue).

Description of selected adverse drug reactions

Hypercholesterolaemia/Hypertriglyceridaemia

In clinical trials of patients with ALK-positive or c-ros oncogene 1 (ROS1)-positive metastatic NSCLC, adverse drug reactions of increase in serum cholesterol or triglycerides were reported in 79.0% and 67.5% of patients, respectively. Mild or moderate adverse drug reactions of hypercholesterolaemia or hypertriglyceridaemia occurred in 59.8% and 47.2% of patients, respectively. No patient was permanently discontinued from treatment with lorlatinib due to hypercholesterolaemia or hypertriglyceridaemia (see Sections 4.2 and 4.4). The median time to onset for hypercholesterolaemia and hypertriglyceridaemia was 15 days and 16 days, respectively. The median duration of hypercholesterolaemia and hypertriglyceridaemia was 526 and 519 days, respectively.

Central nervous system effects

In clinical trials of patients with ALK-positive or c-ros oncogene 1 (ROS1)-positive metastatic NSCLC, CNS adverse drug reactions were primarily cognitive effects (27.4%), mood effects (21.4%), speech effects (8.2%), and psychotic effects (6.9%), and were generally mild, transient, and reversible upon dose delay and/or dose reduction (see Sections 4.2 and 4.4). The most frequent cognitive effect of any grade was memory impairment (10.8%), and the most frequent Grade 3 or 4 reactions were cognitive disorder (0.7%) and confusional state (1.6%). The most frequent mood effect of any grade was anxiety (7.3%), and the most frequent Grade 3 or 4 reactions were irritability (0.7%), depression (0.4%), anxiety, agitation, and bipolar I disorder (0.2% each). The most frequent speech effect of any grade was dysarthria (3.8%), and the Grade 3 or 4 reactions were dysarthria (0.4%), slow speech, and speech disorder (0.2% each). The most frequent psychotic effect of any grade was hallucination (2.7%), and the most frequent Grade 3 or 4 reactions were hallucination auditory, hallucination visual, delusion, acute psychosis, and schizophrenic disorder (0.2% each). Median time to onset for cognitive, mood, speech, and psychotic effects was 129, 57, 58, and 27 days, respectively. Median duration of cognitive, mood, speech, and psychotic effects was 270, 145, 147, and 84 days, respectively.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Clinical studies

Previously untreated ALK-positive advanced NSCLC (CROWN Study)

The efficacy of lorlatinib for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomised, active-controlled, multicenter Study B7461006 (CROWN Study). Patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. Neurologically stable patients with treated or untreated asymptomatic CNS metastases, including leptomeningeal metastases, were eligible. Patients were required to have finished radiation therapy, including stereotactic or partial brain irradiation within 2 weeks prior to randomisation; whole brain irradiation within 4 weeks prior to randomisation.

Patients were randomised 1:1 to receive lorlatinib 100 mg orally once daily or crizotinib 250 mg orally twice daily. Randomisation was stratified by ethnic origin (Asian vs. non-Asian) and the presence or absence of CNS metastases at baseline. Treatment on both arms was continued until disease progression or unacceptable toxicity. The major efficacy outcome measure was progression-free survival (PFS) as determined by Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1). Additional efficacy outcome measures were overall survival (OS), objective response rate (ORR), duration of response (DOR), time to intracranial progression (IC-TTP) all by BICR. In patients with measurable CNS metastases at baseline, additional outcome measures were intracranial objective response rate (IC-ORR) and intracranial duration of response (IC-DOR) all by BICR.

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

Results from the CROWN Study demonstrated a significant improvement in PFS for the LORVIQUA arm over the crizotinib arm. The benefit from lorlatinib treatment was comparable across subgroups of baseline patient and disease characteristics. There was a lower incidence of progression in the CNS as the first site of disease progression, alone or with concurrent systemic progression, 3% in the LORVIQUA arm compared to 24% in the crizotinib arm [hazard ratio (95% CI) for time to cause-specific CNS progression: 0.06 (0.02, 0.18)]. Efficacy results from the CROWN Study as assessed by BICR are summarized in Table 3 and Figure 1. At the data cut-off point OS data was not mature.

Table 3. Overall Efficacy Results in CROWN Study

Efficacy Parameter	**Lorlatinib N=149**	**Crizotinib N=147**
Progression-free survival		
Number of events, n (%)	41 (28%)	86 (59%)
Progressive disease, n (%)	32 (22%)	82 (56%)
Death, n (%)	9 (6%)	4 (3%)
Median, months (95% CI)[a]	NE (NE, NE)	9.3 (7.6, 11.1)
Probability of PFS at 12 months (95% CI)[b]	0.78 (0.70, 0.84)	0.39 (0.30, 0.48)
Hazard ratio (95% CI)[c]	0.28 (0.19, 0.41)	
p-value[*]	<0.0001	
Overall response rate		
Overall response rate (95% CI)[d]	76% (68, 83)	58% (49, 66)
p-value[**]	0.0005	
Complete response	3%	0%
Partial response	73%	58%
Duration of response		
Number of responders, n	113	85
Response duration ≥6 months, n (%)	101 (89%)	53 (62%)
Response duration ≥12 months, n (%)	79 (70%)	23 (27%)
Response duration ≥18 months, n (%)	34 (30%)	9 (11%)

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

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

[**] p-value based on 1-sided Cochran-Mantel-Haenszel test.

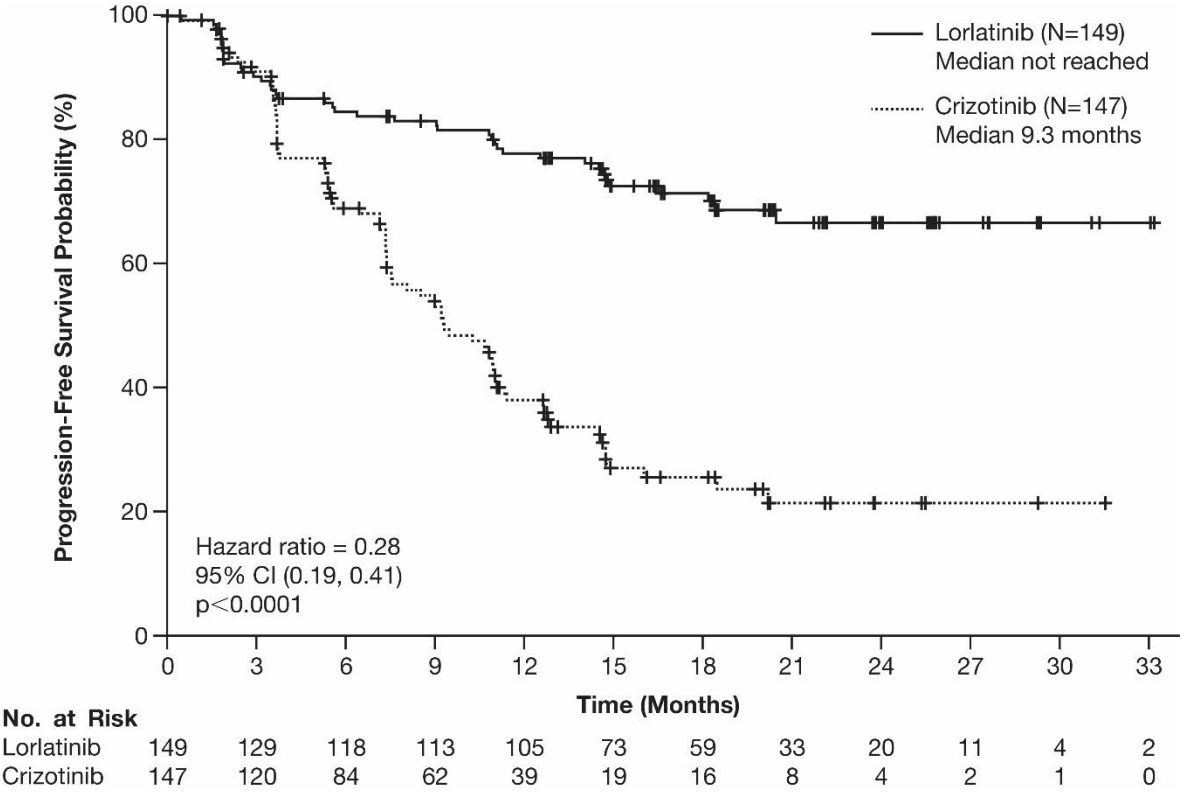
[a] Based on the Brookmeyer and Crowley method.

[b] CIs were derived using the log-log transformation with back transformation to original scale.

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

[d] Using exact method based on binomial distribution.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival by Blinded Independent Central Review in CROWN Study



The results of prespecified exploratory analyses of intracranial response rate in 30 patients with measurable CNS lesions at baseline as assessed by BICR are summarized in Table 4. Of these, no patients received prior brain radiation.

Table 4. Intracranial Responses in Patients with Measurable Intracranial Lesions at Baseline in CROWN Study

Intracranial Tumor Response Assessment	**Lorlatinib N=17**	**Crizotinib N=13**
Intracranial response rate (95% CI)[a]	82% (57, 96)	23% (5, 54)
Complete response	71%	8%
Partial response	12%	15%
Duration of response		
Number of responders, n	14	3
Response duration ≥12 months, n (%)	11 (79%)	0

Abbreviations: CI=confidence interval; N/n=number of patients.
[a] Using exact method based on binomial distribution.

Patient-reported functioning, symptoms, and global quality of life (QoL) were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30 and its corresponding lung cancer module (EORTC QLQ-LC13) as well as the EuroQol 5 dimension 5 level (EQ-5D-5L) questionnaire. Completion rates were 100% at baseline and remained ≥96% through cycle 18.

Mean baseline scores in global QoL were 64.6 (SE±1.82) in the lorlatinib arm and 59.8 [standard error (SE)±1.90] in the crizotinib arm. Lorlatinib treatment resulted in a

numerically greater improvement in patient-reported global QoL compared with crizotinib treatment in previously untreated ALK-positive NSCLC patients: mean difference=4.65 [95% CI: 1.14, 8.16; p-value (2-sided)=0.0096].

Time-to-Deterioration (TTD) was prespecified as time between baseline and first occurrence of ≥10 points increase from baseline in the composite endpoint of pain in chest, dyspnea, and cough symptom scores. TTD in the composite endpoint of lung cancer symptoms (cough, dyspnea, or pain in chest) was not different between treatment arms [HR=1.09, 95% CI: 0.82, 1.44; p-value (2-sided)=0.5415].

ALK-positive advanced NSCLC previously treated with an ALK kinase inhibitor

The use of LORVIQUA in the treatment of ALK-positive advanced NSCLC previously treated with 1 or more ALK TKIs was investigated in Study B7461001, a single-arm, multicenter Phase 1/2 study and in Study B7461027, a single-arm, multicentre Phase 4 study. In Study B7461001, a total of 197 patients with ALK-positive advanced NSCLC previously treated with 1 or more ALK TKIs were enrolled in the Phase 2 portion of the study. In Study B7461027, a total of 71 patients with ALK-positive advanced NSCLC after one prior ALK TKI treatment (alectinib or ceritinib) were enrolled. In both studies, patients received LORVIQUA orally at the recommended dose of 100 mg once daily, continuously.

In Study B7461001, the primary efficacy endpoint in the Phase 2 portion of the study was ORR, including intracranial ORR, as per Independent Central Review (ICR) according to modified Response Evaluation Criteria in Solid Tumors (modified RECIST v 1.1). Secondary endpoints included DOR, intracranial DOR, time-to-tumor response (TTR), and progression-free survival (PFS). In Study B7461027, the primary efficacy endpoint was ORR, as per ICR according to RECIST v1.1. Secondary endpoints included IC-ORR, DOR, IC-DOR, time-to-tumour response (TTR), time-to-tumour progression (TTP) and PFS.

Patient demographics of the 197 ALK-positive advanced NSCLC patients previously treated with 1 or more ALK TKIs in Study B7461001 were 59% female, 49% Caucasian, 36% Asian and the mean age was 53 years (range: 29 to 85 years) with 19% ≥65 years of age. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 or 1 in 97% of patients and 2 in 4% of patients. Brain metastases were present at baseline in 62% of patients. All 197 patients had received prior systemic therapy, 20% received 1, 28% received 2, 19% received 3, and 34% received 4 or more prior systemic therapies. Of the 197 patients, 44% received 1 prior ALK TKI, 33% received 2 prior ALK TKIs, and 23% received 3 or more prior ALK TKIs.

Patient demographics of the 71 ALK positive advanced NSCLC patients who progressed after treatment with one prior ALK TKI (alectinib or ceritinib) with or without chemotherapy in Study B7461027 were 42% female, 76% White, 21% Asian, and the median age was 59 years (range: 26 to 87 years) with 32% of patients ≥65 years of age. The ECOG performance status at baseline was 0 in 52% or 1 in 48% of patients. Brain metastases were present at baseline in 42% of patients. Of the 71 patients, 85% received alectinib and 16% received ceritinib as their prior ALK TKIs.

The main efficacy results for Study B7461001 and Study B7461027 are included in Tables 5 and 6.

Table 5. Efficacy Results in Study B7461001 and Study B7461027 by Prior ALK TKI Treatment

Efficacy Parameter	Group A	Group B	Group C	Pooled Groups A, B, C
	Crizotinib (N = 59)	One 2nd generation ALK TKI[a] (N = 99)	Two or more ALK TKIs (N = 111)	One or more ALK TKIs (N = 269)
Objective response rate[b] (95% CI)[c]	69.5% (56.1, 80.8)	42.4% (32.5, 52.8)	38.7% (29.6, 48.5)	48.0% (41.9, 54.1)
Complete response, n	1	5	2	8
Partial response, n	40	37	41	121
Duration of response Median, months (95% CI)[d]	NR (11.1, NR)	NR (7.8, NR)	NR (5.5, NR)	12.6 (8.4, NR)
Progression-free survival Median, months (95% CI)[d]	NR (12.5, NR)	8.3 (6.3, 16.5)	6.9 (5.4, 9.5)	8.2 (6.9, 11.1)

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

[a] Alectinib, brigatinib, or ceritinib.

[b] Per ICR.

[c] Using exact method based on binomial distribution.

[d] Using the Brookmeyer and Crowley method.

Table 6. Intracranial Efficacy Results in Study B7461001 and Study B7461027 by Prior Treatment

Efficacy Parameter	Group A	Group B	Group C	Pooled Groups A, B, C
	Crizotinib (N = 37)	One 2nd generation ALK TKI[a] (N = 43)	Two or more ALK TKIs (N = 81)	One or more ALK TKIs (N = 161)
Objective response rate[b] (95% CI)[c]	70.3% (53.0, 84.1)	46.5% (31.2, 62.3)	48.1% (36.9, 59.5)	52.8% (44.8, 60.7)
Complete response, n	11	12	24	47
Partial response, n	15	8	15	38
Duration of response Median, Months (95% CI)[d]	NR (19.4, NR)	NR (NR, NR)	14.5 (11.1, NR)	NR (15.0, NR)

Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; ICR=Independent Central Review; N/n=number of patients; NSCLC=non-small cell lung cancer; NR=not reached; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

[a] Alectinib, brigatinib, or ceritinib.

[b] Per ICR.

[c] Using exact method based on binomial distribution.

[d] Using the Brookmeyer and Crowley method.

Among the 129 patients with a confirmed objective response by ICR, the median TTR was 1.4 months (range: 1.1 to 16.6 months). Among the 85 patients with a confirmed objective tumor response by ICR, the median intracranial-TTR was 1.4 months (range: 1.1 to 16.2 months).

5.2 Pharmacokinetic properties

Absorption

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

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

Administration of lorlatinib with a high fat, high calorie meal resulted in 5% higher exposure compared to overnight fasting (AUC_{inf} ratio of 104.7%; 90% CI for the ratio: 101.3%, 108.3%). Lorlatinib may be administered with or without food. The proton-pump inhibitor rabeprazole had a minimal effect on lorlatinib plasma exposure (AUC_{inf} ratio of 100.9%; 90% CI for the ratio: 97.6%, 104.3%). No dose adjustment is recommended when lorlatinib is taken with proton-pump inhibitors, H_2-receptor antagonists or locally-acting antacids.

Steady-state lorlatinib C_{max} increased dose-proportionally and AUC_{tau} increased slightly less than proportionally over the dose range of 10 to 200 mg once daily. At the 100 mg once daily lorlatinib dose, the geometric mean peak plasma concentration was 577 ng/mL and the AUC_{24} 5650 ng·h/mL in patients with cancer. The geometric mean oral clearance was 17.7 L/h. Lorlatinib oral clearance increased at steady-state compared to single dose, indicating autoinduction.

Distribution

In vitro binding of lorlatinib to human plasma proteins is 66% with moderate binding to albumin to α_1-acid glycoprotein.

Metabolism

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

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

Elimination

The plasma half-life of lorlatinib after a single 100 mg dose was 23.6 hours. Following oral administration of a 100 mg radiolabeled dose of lorlatinib, a mean 47.7% of the radioactivity was recovered in urine and 40.9% of the radioactivity was recovered in feces, with overall mean total recovery of 88.6%.

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

Cardiac electrophysiology

QT interval

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

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

In 295 patients who received lorlatinib at the recommended dose of 100 mg once daily in Study B7461001, no large mean increases from baseline in the QTcF interval (i.e., >20 ms) were detected.

PR interval

In 295 patients who received lorlatinib at the recommended dose of 100 mg once daily and had a ECG measurement in Study B7461001, the maximum mean change from baseline for PR interval was 16.4 ms (2-sided 90% upper CI: 19.4 ms). Among the 284 patients with PR interval <200 ms, 14% had PR interval prolongation ≥200 ms after starting lorlatinib. The prolongation of PR interval occurred in a concentration-dependent manner. Atrioventricular block occurred in 1.0% of patients.

For those patients who develop PR prolongation, dose modification may be required (see Section 4.2).

Special populations

Hepatic impairment

As lorlatinib is metabolized in the liver, hepatic impairment is likely to increase lorlatinib plasma concentrations. Clinical studies that were conducted excluded patients with AST or ALT >2.5 × ULN, or if due to underlying malignancy, >5.0 × ULN or with total bilirubin >1.5 × ULN. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild hepatic impairment (n=50). No dose adjustments are recommended for patients with mild or moderate hepatic impairment (see Section 4.2). In a hepatic impairment study following administration of a single oral 100 mg dose of LORVIQUA, lorlatinib AUC_{inf} increased by 15% and 82% in patients with moderate hepatic impairment (Child-Pugh B) and severe hepatic impairment (Child-Pugh C), respectively, compared to subjects with normal hepatic function.

Renal impairment

Less than 1% of the administered dose is detected as unchanged lorlatinib in urine. Clinical studies excluded patients with serum creatinine >1.5 × ULN or estimated CL_{cr} <60 mL/min. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild (n=103) or moderate (n=41) renal impairment (CL_{cr} ≥30 mL/min). Based on a renal impairment study, no dose adjustments are recommended for patients with mild or moderate renal impairment [absolute eGFR based on Modification of Diet in Renal Disease Study equation (MDRD)-derived eGFR (in mL/min/1.73 m^2) × measured body surface area/1.73 ≥30 mL/min]. In this study, lorlatinib AUC_{inf} increased by 41% in subjects with severe renal impairment (absolute eGFR <30 mL/min) compared to subjects with normal renal function (absolute eGFR ≥90 mL/min). A reduced dose of LORVIQUA is recommended in patients with severe renal impairment, e.g., a starting dose of 75 mg taken orally once daily (see Section 4.2).

Elderly (≥65 years)

Out of the 476 patients who received lorlatinib 100 mg orally once daily in Study B7461001 (N=327) and Study B7461006 (N=149), 25% of patients were aged 65 years or older. Of the 215 patients in the efficacy population in Study B7461001, 17.7% of patients were aged 65 years or older, and of the 149 patients in the lorlatinib arm of the CROWN Study, 40% were aged 65 years or older. No clinically relevant differences in safety or efficacy were observed between patients aged greater than or equal to 65 years of age and younger patients; no dose adjustments are recommended in elderly patients (see Section 4.2).

Gender, race, body weight, and phenotype

Population pharmacokinetic analyses in patients with advanced NSCLC and healthy volunteers indicate that there are no clinically relevant effects of age, gender, race, body weight, or phenotypes for CYP3A5 and CYP2C19.

5.3 Preclinical safety data

Repeat-dose toxicity

The main toxicities observed were inflammation across multiple tissues (with increases in white blood cells), and changes in the pancreas (with increases in amylase and lipase), hepatobiliary system (with increases in liver enzymes), male reproductive system, cardiovascular system, kidneys and gastrointestinal tract, and peripheral nerves and the CNS (potential for cognitive functional impairment) (approximately 4.6 to 21 times the human clinical exposure at 100 mg based on AUC for all toxicities). Changes in blood pressure and heart rate, and QRS and PR interval prolongation were also observed in animals after acute dosing (approximately 2.6 times the human clinical exposure at 100 mg after a single dose based on C_{max}). All target organ findings with the exception of the hepatic bile duct hyperplasia (approximately 7.1 to 21 times the human clinical exposure at 100 mg based on AUC) were partially to fully reversible.

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies have not been conducted with lorlatinib.

Reproductive toxicity

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline Cellulose
Dibasic Calcium Phosphate Anhydrous
Sodium Starch Glycolate
Magnesium Stearate

Film-coating
HPMC 2910/Hypromellose (E464)
Lactose Monohydrate
Macrogol 4000/PEG 3350 (E1521)
Triacetin
Titanium Dioxide (E171)
Ferrosoferric Oxide/Iron Oxide Black (E172)
Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Refer to outer box for Expiry Date.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminum foil blister with aluminum foil lidding

Pack sizes:

- LORVIQUA Film-coated Tablet 100 mg x 10s
- LORVIQUA Film-coated Tablet 100 mg x 30s
- LORVIQUA Film-coated Tablet 25 mg x 30s
- LORVIQUA Film-coated Tablet 25 mg x 60s

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

LOR-SIN-0825/1
Date of last revision: April 2026

Package leaflet: Information for the user

LORVIQUA film-coated tablet 25 mg
LORVIQUA film-coated tablet 100 mg
lorlatinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LORVIQUA is and what it is used for

What LORVIQUA is
LORVIQUA contains the active substance lorlatinib, a medicine that is used for treatment of adults with advanced stages of a form of lung cancer called non-small cell lung cancer (NSCLC). LORVIQUA belongs to the group of medicines that inhibit an enzyme called anaplastic lymphoma kinase (ALK). LORVIQUA is only given to patients who have an alteration in the ALK gene, see **How LORVIQUA works** below.

What LORVIQUA is used for
LORVIQUA can be prescribed to you if:
- your NSCLC is ALK-positive – this means your cancer cells have a fault in a gene that makes an enzyme ALK; you have not received any prior treatment for advanced ALK-positive NSCLC; or
- you have been previously treated with crizotinib followed by at least one other ALK inhibitor; or
- you have been previously treated with a medicine called alectinib or ceritinib, which are ALK inhibitors.

How LORVIQUA works
LORVIQUA inhibits a type of enzyme called tyrosine kinase and triggers the death of cancer cells in patients with alterations in genes for ALK. LORVIQUA is only given to patients whose disease is due to an alteration in the gene for ALK tyrosine kinase.

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

2. What you need to know before you take LORVIQUA

Do not take LORVIQUA
- if you are allergic to lorlatinib or any of the other ingredients of this medicine (listed in section 6).
- if you are taking any of these medicines or herbal products:
  - rifampin (used to treat tuberculosis)
  - carbamazepine, phenytoin (used to treat epilepsy)
  - enzalutamide (used to treat prostate cancer)
  - mitotane (used to treat cancer of the adrenal glands)
  - St. John's wort (*Hypericum perforatum*, a herbal preparation).

Warnings and precautions
Talk to your doctor before taking LORVIQUA:
- if you have high levels of blood cholesterol or triglycerides.
- if you have high levels of the enzymes known as amylase or lipase in the blood or a condition such as pancreatitis that can raise the levels of these enzymes.
- if you have problems with your heart, including heart failure, slow heart rate, or if electrocardiogram (ECG) results show that you have an abnormality of the electrical activity of your heart known as prolonged PR interval or AV block.
- if you have cough, chest pain, shortness of breath, or worsening of respiratory symptoms or have ever had a lung condition called pneumonitis.
- if you have high blood pressure.
- if you have high blood sugar.

If you are not sure, talk to your doctor, pharmacist or nurse before taking LORVIQUA.

Tell your doctor immediately if you develop:
- heart problems. Tell your doctor right away about changes in your heartbeat (fast or slow), light-headedness, fainting, dizziness or shortness of breath. These symptoms could be signs of heart problems. Your doctor may check for problems with your heart during treatment with LORVIQUA. If the results are abnormal, your doctor may decide to reduce the dose of LORVIQUA or stop your treatment.
- speech problems, difficulty speaking, including slurred or slow speech. Your doctor may investigate further and may decide to reduce your dose of LORVIQUA or stop your treatment.
- mental status changes, mood or memory problems, such as change in your mood (including depression, euphoria and mood swings), irritability, aggression, agitation, anxiety or a change in your personality and episodes of confusion or loss of contact with reality, such as believing, seeing or hearing things that are not real. Your doctor may investigate further and may decide to reduce your dose of LORVIQUA or stop your treatment.
- pain in the back or abdomen (belly), yellowing of the skin and eyes (jaundice), nausea or vomiting. These symptoms could be signs of pancreatitis. Your doctor may investigate further and may decide to modify the treatment base on the findings.
- cough, chest pain, or a worsening of existing respiratory symptoms. Your doctor may investigate further and treat you with other medicines such as antibiotics and steroids. Your doctor may decide to temporary or permanently halt your treatment with LORVIQUA.
- headaches, dizziness, blurred vision, chest pain or shortness of breath. These symptoms could be signs of high blood pressure. Your doctor may investigate further and treat you with medicines to control your blood pressure. Your doctor may decide to reduce your dose of LORVIQUA or stop your treatment.
- feeling very thirsty, a need to urinate more than usual, feeling very hungry, feeling sick to your stomach, weakness or tiredness, or confusion. These symptoms could be signs of high blood sugar. Your doctor may investigate further and initiate therapies to control your blood sugar. Your doctor may decide to reduce your dose of LORVIQUA or stop your treatment.

Your doctor may do further assessments and may decide to reduce the starting dose of LORVIQUA or stop your treatment if you:
- have pre-existing liver problems.
- have pre-existing kidney problems.

See **Possible side effects** in section 4 for more information.

Children and adolescents
This medicine is only indicated in adults and it is not to be given to children and adolescents.

Tests and checks
You will have blood tests before you start treatment and during your treatment. These tests are to check the level of cholesterol, triglycerides and the enzymes amylase or lipase in your blood before you start treatment with LORVIQUA and regularly during treatment.

Other medicines and LORVIQUA
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicines obtained over the counter. This is because LORVIQUA can affect the way some other medicines work. Also some medicines can affect the way LORVIQUA works.

You must not take LORVIQUA with certain medicines. These are listed under **Do not take LORVIQUA**, at the start of section 2.

In particular tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- boceprevir, telaprevir – a medicine used to treat hepatitis C.
- dihydroergotamine, ergotamine – medicines used to treat migraine headaches.
- cobicistat, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either danoprevir, elvitegravir, indinavir, lopinavir, saquinavir or tipranavir – medicines used to treat AIDS/HIV.
- ketoconazole, itraconazole, voriconazole, posaconazole – medicines used to treat fungal infections. Also troleandomycin, a medicine used to treat certain types of bacterial infections.
- quinidine – a medicine used to treat irregular heartbeat and other heart problems.
- pimozide – a medicine used to treat mental health problems.
- alfentanil and fentanyl – medicines used to treat severe pain.
- cyclosporine, sirolimus, and tacrolimus – medicines used in organ transplantation to prevent organ rejection.
- hormonal contraceptives.
- conivaptan is used to treat hyponatremia (low sodium levels).
- digoxin is used to treat heart failure.

LORVIQUA with food and drink
You must not drink grapefruit juice or eat grapefruit while on treatment with LORVIQUA as they may change the amount of LORVIQUA in your body.

Pregnancy, breast-feeding and fertility

Contraception – information for women
You should not become pregnant while taking this medicine. If you are able to have children, you must use highly effective contraception (for example, double-barrier contraception such as condom and diaphragm) while on treatment and for at least 21 days after stopping treatment. Lorlatinib may reduce the effectiveness of hormonal contraceptive methods (for example, birth control pill); therefore, hormonal contraceptives may not be considered highly effective. If hormonal contraception is unavoidable it must be used in combination with a condom. Talk to your doctor about the right methods of contraception for you and your partner.

Contraception – information for men

You should not father children during treatment with LORVIQUA because this medicine could harm the baby. If there is any possibility that you may father a child while taking this medicine, you must use a condom during treatment, and for at least 97 days after completing therapy. Talk to your doctor about the right methods of contraception for you and your partner.

Pregnancy

- Do not take LORVIQUA if you are pregnant. This is because it may harm your baby.
- If your male partner is being treated with LORVIQUA, he must use a condom during treatment and for at least 97 days after completing therapy.
- If you become pregnant when taking the medicine or during the 21 days after taking your last dose, tell your doctor straight away.

Breast-feeding

Do not breast-feed while taking this medicine and for 7 days after the last dose. This is because it is not known if LORVIQUA can pass into breast milk and could therefore harm your baby.

Fertility

LORVIQUA may affect male fertility. Talk to your doctor about fertility preservation before taking LORVIQUA.

Driving and using machines

You should take special care when driving and using machines when taking LORVIQUA because of its effects on your mental state.

LORVIQUA contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

LORVIQUA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 25 mg or 100 mg tablet, that is to say essentially 'sodium-free'.

3. How to take LORVIQUA

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

- The recommended dose is one tablet of 100 mg taken by mouth once daily.
- Take the dose at about the same time each day.
- You can take the tablets with food or between meals always avoiding grapefruit and grapefruit juice.
- Swallow the tablets whole and do not crush, chew or dissolve the tablets.
- Sometimes your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely if you feel unwell.

If you vomit after taking LORVIQUA

If you vomit after taking a dose of LORVIQUA, do not take an extra dose, just take your next dose at the usual time.

If you take more LORVIQUA than you should

If you accidentally take too many tablets, tell your doctor, pharmacist or nurse right away. You may require medical attention.

If you forget to take LORVIQUA

What to do if you forget to take a tablet depends on how long it is until your next dose.

- If your next dose is in 4 hours or more, take the missed tablet as soon as you remember. Then take the next tablet at the usual time.

- If your next dose is in less than 4 hours away, skip the missed tablet. Then take the next tablet at the usual time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking LORVIQUA
It is important to take LORVIQUA every day, for as long as your doctor asks you to. If you are not able to take the medicine as your doctor has prescribed, or you feel you do not need it anymore, speak with your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious.

Tell your doctor straight away if you notice any of the following side effects (also section 2 **What you need to know before you take LORVIQUA).** Your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely:
- cough, shortness of breath, chest pain or worsening breathing problems
- slow pulse, (50 beats per minute or less), feeling tired, dizzy or faint or losing consciousness
- abdominal (belly) pain, back pain, nausea, vomiting, fever, rapid pulse or yellowing of the skin and eyes
- mental status changes; changes in cognition including confusion, memory loss, reduced ability to concentrate; changes in mood including irritability and mood swings; changes in speech including difficulty speaking, such as slurred or slow speech; or loss of contact with reality, such as believing, seeing or hearing things that are not real

Other side effects of LORVIQUA may include:

- increase in cholesterol and triglycerides (fats in your blood that would be detected during blood tests)
- increase in blood sugar
- peripheral neuropathy (nerve damage in arms and legs - causing pain or numbness, burning and tingling)
- sleep effects (including abnormal dreams, insomnia, nightmare, sleep disorder, sleep talking, somnambulism)
- seizures
- problems with your eyes, such as difficulty seeing out of one or both eyes, double vision, or perceived flashes of light
- high blood pressure
- diarrhoea
- constipation
- pain in your joints
- swelling
- tiredness
- increased level of enzymes called lipase and/or amylase in the blood that would be detected during blood tests
- weight gain

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LORVIQUA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister foil and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the package is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What LORVIQUA contains
- The active substance is lorlatinib.
  LORVIQUA Film-coated Tablet 25 mg: each film-coated tablet (tablet) contains 25 mg lorlatinib.
  LORVIQUA Film-coated Tablet 100 mg: each film-coated tablet (tablet) contains 100 mg lorlatinib.

- The other ingredients are:
  Tablet core: Microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, magnesium stearate.
  Film-coating: HPMC 2910/Hypromellose (E464), lactose monohydrate, macrogol 4000/PEG 3350 (E1521), triacetin, titanium dioxide (E171), ferrosoferric oxide/iron oxide Black (E172), and iron oxide red (E172).

See **LORVIQUA contains lactose** and **LORVIQUA contains sodium** in section 2.

What LORVIQUA looks like and contents of the pack
LORVIQUA Film-coated Tablet 25 mg is supplied as 8 mm round tan immediate release film-coated tablets, debossed with "Pfizer" on one side and "25" and "LLN" on the other side.
LORVIQUA Film-coated Tablet 25 mg is provided in blisters of 10 tablets, which are available in packs containing 30 tablets (3 blisters) or 60 tablets (6 blisters).

LORVIQUA Film-coated Tablet 100 mg is supplied as oval (8.5 × 17 mm) lavender immediate release film-coated tablets, debossed with "Pfizer" on one side and "LLN 100" on the other side.
LORVIQUA Film-coated Tablet 100 mg is provided in blisters of 10 tablets, which are available in packs containing 10 tablets (1 blister) or 30 tablets (3 blisters).

Not all pack sizes may be marketed.

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