PFIZER
LORVIQUA®

1. NAME OF THE MEDICINAL PRODUCT

LORVIQUA 25 MG FILM COATED TABLETS
LORVIQUA 100 MG FILM COATED TABLETS

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 as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

LORVIQUA as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after:
- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
- crizotinib and at least one other ALK TKI.

4.2 Posology and Method of Administration

Treatment with lorlatinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

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 utilized. 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 as long as the patient is deriving clinical benefit from therapy.

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) OR Moderate hypercholesterolaemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L)	Introduce or modify lipid-lowering therapy[a] in accordance with respective prescribing information; continue LORVIQUA at same dose.
Mild hypertriglyceridaemia (triglycerides between 150 and 300	

Adverse Drug Reaction	LORVIQUA Dosing
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 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.
Lipase/Amylase increase	
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at 1 reduced dose level.
Pneumonitis	
Grade 1: Mild OR	Withhold lorlatinib until symptoms have returned to baseline and consider initiating

Adverse Drug Reaction	LORVIQUA Dosing
Grade 2: Moderate	corticosteroids. Resume lorlatinib at 1 reduced dose level. Permanently discontinue lorlatinib if ILD/pneumonitis recurs or fails to recover after 6 weeks of lorlatinib hold and steroid treatment.
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.
PR interval prolongation/Atrioventricular (AV) block	
First-degree AV block: Asymptomatic	Continue lorlatinib 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 lorlatinib. 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 lorlatinib at 1 reduced dose level.
Second-degree AV block: Asymptomatic	Withhold lorlatinib. 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. If subsequent ECG does not show second-degree AV block, resume lorlatinib at 1 reduced dose level.
Second-degree AV block: Symptomatic	Withhold lorlatinib. 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 lorlatinib at 1 reduced dose level.
Complete AV block	Withhold lorlatinib. 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.

Adverse Drug Reaction	LORVIQUA Dosing
	If pacemaker placed, resume lorlatinib at full dose. If no pacemaker placed, resume lorlatinib 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.
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.
Hyperglycemia	
Grade 3 OR Grade 4 (Persistent hyperglycemia greater than 250 mg/dL despite optimal anti-hyperglycemic therapy)	Withhold LORVIQUA until hyperglycemia is adequately controlled, then resume LORVIQUA at the next lower dosage. If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue LORVIQUA.
Other adverse drug reactions[c]	
Grade 1: Mild OR Grade 2: Moderate	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3: Severe	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).

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

4.3 Contraindications

Hypersensitivity to lorlatinib or to any of the excipients listed in Section 6.1.

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

Hyperlipidemia

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 psychotic effects, changes in cognitive function, mood, speech, and mental status changes (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).

Left ventricular ejection fraction decrease

Left ventricular ejection fraction (LVEF) decrease has been reported in patients receiving lorlatinib who had baseline and at least one follow-up LVEF assessment. Based on the available clinical study data, it is not possible to determine a causal relationship between effects on changes in cardiac contractility and lorlatinib. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including LVEF assessment at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring, including LVEF assessment, should be considered.

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 169 days (range: 1 to 1755 days) and 158 days (range: 1 to 1932 days), respectively. Risk of pancreatitis should be considered in patients receiving lorlatinib due to concomitant hypertriglyceridemia 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).

Pneumonitis

Severe or life-threatening pulmonary adverse drug reactions consistent with pneumonitis have occurred with lorlatinib (see Section 4.8). Any patient who presents with worsening of respiratory symptoms indicative of pneumonitis (e.g., dyspnea, cough, and fever) should be promptly evaluated for 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).

Hyperglycemia

Hyperglycemia 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) 42% and C_{max} 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 the safety profile

The most frequently reported adverse reactions were hypercholesterolaemia (79.0%), hypertriglyceridaemia (67.5%), oedema (55.4%), peripheral neuropathy (44.2%), fatigue (30.7%), weight increased (29.8%), arthralgia (27.8%), cognitive effects (27.4%), diarrhoea (22.7%) and mood effects (21.4%).

Serious adverse 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 reactions occurred in 20.1% of patients receiving lorlatinib. The most common adverse reactions that led to dose reductions were

oedema, cognitive effects and peripheral neuropathy. Permanent treatment discontinuation associated with adverse reactions occurred in 4.0% of patients receiving lorlatinib. The most frequent adverse reactions that led to permanent discontinuations were cognitive effects, peripheral neuropathy, pneumonitis and psychotic effects.

Tabulated list of adverse reactions

Table 2 presents adverse reactions occurring in 547 adult patients treated with lorlatinib 100 mg once daily with advanced NSCLC from Study A (N=327), CROWN study (N=149) and Study B (N=71).

The adverse reactions listed in Table 2 are presented by system organ class and frequency categories, defined using the following convention: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing medical seriousness.

Table 2. Adverse Reactions

System organ class and adverse reaction	**Frequency category**	**All Grades %**	**Grades 3-4 %**
Blood and lymphatic system disorders			
Anaemia	Very common	19.6	4.4
Metabolism and nutrition disorders			
Hypercholesterolaemia[a]	Very common	79.0	19.2
Hypertriglyceridaemia[b]	Very common	67.5	20.3
Hyperglycaemia	Common	9.7	3.7
Psychiatric disorders			
Mood effects[c]	Very common	21.4	1.3
Psychotic effects[d]	Common	6.9	0.9
Mental status changes	Common	1.1	0.9
Nervous system disorders			
Cognitive effects[e]	Very common	27.4	3.5
Peripheral neuropathy[f]	Very common	44.2	2.6
Headache	Very common	18.6	0.7
Speech effects[g]	Common	8.2	0.7
Eye disorders			
Vision disorder[h]	Very common	16.1	0.2
Vascular disorders			
Hypertension	Very common	14.8	6.0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis[i]	Common	2.4	0.7
Gastrointestinal disorders			
Diarrhoea	Very common	22.7	1.8
Nausea	Very common	17.6	0.9
Constipation	Very common	16.8	0.2
Skin and subcutaneous tissue disorders			
Rash[j]	Very common	14.6	0.2

System organ class and adverse reaction	Frequency category	All Grades %	Grades 3-4 %
Renal and urinary disorders			
Proteinuria	Common	3.7	0.4
Musculoskeletal and connective tissue disorders			
Arthralgia	Very common	27.8	0.7
Myalgia[k]	Very common	15.0	0
General disorders and administration site conditions			
Oedema[l]	Very common	55.4	2.9
Fatigue[m]	Very common	30.7	1.1
Investigations			
Weight increased	Very common	29.8	11
Lipase increased	Very common	12.8	6.8
Amylase increased	Very common	11.3	2.7
Electrocardiogram PR prolongation	Uncommon	0.7	0

Adverse reactions that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. Terms actually reported in the studies and contributing to the relevant adverse 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).
[d] Psychotic effects (including auditory hallucination, hallucination, visual hallucination).
[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 disorder.
[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 (dysarthria, slow speech, speech disorder).
[h] Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).
[i] Pneumonitis (including interstitial lung disease, lung opacity, pneumonitis).
[j] Rash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash).
[k] Myalgia (including musculoskeletal pain, myalgia).
[l] Oedema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).
[m] Fatigue (including asthenia, fatigue).

Description of selected adverse reactions

Hypercholesterolaemia/Hypertriglyceridaemia

Adverse reactions of increase in serum cholesterol or triglycerides were reported in 79.0% and 67.5% of patients, respectively. Of those, mild or moderate adverse reactions of hypercholesterolaemia or hypertriglyceridaemia occurred in 59.8% and 47.2% of patients, respectively (see Section 4.4). The median time to onset for hypercholesterolaemia and hypertriglyceridaemia was 15 days (range: 1 to 1921 days) and 16 days (range: 1 to 1921 days), respectively. The median duration of hypercholesterolaemia and hypertriglyceridaemia was 526 and 519 days, respectively.

Central nervous system effects
CNS adverse 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 spontaneously 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 confusional state and cognitive disorder (1.6% and 0.7%, respectively). The most frequent mood effect of any grade was anxiety (7.3%), and the most frequent Grade 3 and 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.

Hypertension
Adverse reactions of hypertension were reported in 14.8% of patients from Study A, CROWN (B7461006) and Study B (B7461027). Of those, mild or moderate adverse reactions of hypertension occurred in 8.8% of patients (see Section 4.4). The median time to onset of hypertension was 295 days (range: 1 to 1990 days). The median duration of hypertension was 505 days.

Hyperglycaemia
Adverse reactions of hyperglycaemia were reported in 9.7% of patients from Study A, CROWN (B7461006) and Study B (B7461027). Of those, mild or moderate adverse reactions of hyperglycaemia occurred in 6.0% of patients (see Section 4.4). The median time to onset of hyperglycaemia was 148 days (range: 1 to 1637 days). The median duration of hyperglycaemia was 118 days.

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

Pharmacotherapeutic group: anti-neoplastic agents, protein kinase inhibitors, ATC code: L01ED05

Mechanism of action

Lorlatinib is a selective, adenosine triphosphate (ATP)-competitive inhibitor of ALK and c-ros oncogene 1 (ROS1) tyrosine kinases.

In non-clinical studies, lorlatinib inhibited catalytic activities of non-mutated ALK and clinically relevant ALK mutant kinases in recombinant enzyme and cell-based assays. Lorlatinib demonstrated marked antitumour activity in mice bearing tumour 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 alectinib, brigatinib, ceritinib, and crizotinib. Lorlatinib was also capable of penetrating the blood-brain barrier. Lorlatinib demonstrated activity in mice bearing orthotopic EML4-ALK or EML4-ALK^{L1196M} brain tumour implants.

Clinical efficacy

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, multicentre Study B7461006 (CROWN Study). Patients were required to have an Eastern Cooperative Oncology Group (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 Tumours (RECIST) version 1.1 (v1.1). Additional efficacy outcome measures were overall survival (OS), PFS by investigator assessment, PFS2 and tumour assessment related data by BICR, including objective response rate (ORR), duration of response (DOR) and time to intracranial progression (IC-TTP). In patients with 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%). Central nervous system 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 are summarised in Table 3. At the data cutoff point, OS and PFS2 data were not mature.

Table 3. Overall Efficacy Results in CROWN Study

Efficacy parameter	Lorlatinib N=149	Crizotinib N=147
Median duration of follow-up, months (95% CI)[a]	18 (16, 20)	15 (13, 18)
Progression-free survival by BICR		
Number of patients with event, 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 (8, 11)
Hazard ratio (95% CI)[b]	0.28 (0.19, 0.41)	
p-value[*]	< 0.0001	
Overall survival		
Number of patients with event, n (%)	23 (15%)	28 (19%)
Median, months (95% CI)[a]	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[b]	0.72 (0.41, 1.25)	
Progression-free survival by INV		
Number of patients with event, n (%)	40 (27%)	104 (71%)
Progressive disease, n (%)	34 (23%)	99 (67%)
Death, n (%)	6 (4%)	5 (3%)
Median, months (95% CI)[a]	NE (NE, NE)	9 (7, 11)
Hazard ratio (95% CI)[b]	0.21 (0.14, 0.31)	
p-value[*]	< 0.0001	
Overall response by BICR		
Overall response rate, n (%)	113 (76%)	85 (58%)
(95% CI)[c]	(68, 83)	(49, 66)
Time to intracranial progression		
Median, months (95% CI)[a]	NE (NE, NE)	16.6 (11, NE)
Hazard ratio (95% CI)[b]	0.07 (0.03, 0.17)	
Duration of response		
Number of responders	113	85
Median, months (95% CI)[a]	NE (NE, NE)	11 (9, 13)
Intracranial overall response in patients with measurable CNS lesions at baseline	N=17	N=13
Intracranial response rate, n (%)	14 (82%)	3 (23%)
(95% CI)[c]	(57, 96)	(5, 54)
Complete response rate	71%	8%
Duration of response		
Number of responders	14	3
Median, months (95% CI)[a]	NE (NE, NE)	10 (9, 11)
Intracranial overall response in patients with any measurable or nonmeasurable CNS lesions at baseline	N=38	N=40
Intracranial response rate, n (%)	25 (66%)	8 (20%)
(95% CI)[c]	(49, 80)	(9, 36)
Complete response rate	61%	15%
Duration of response		
Number of responders	25	8
Median, months (95% CI)[a]	NE (NE, NE)	9 (6, 11)

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CNS=central nervous system; INV=investigator assessment; N/n=number of patients; NE=not estimable.

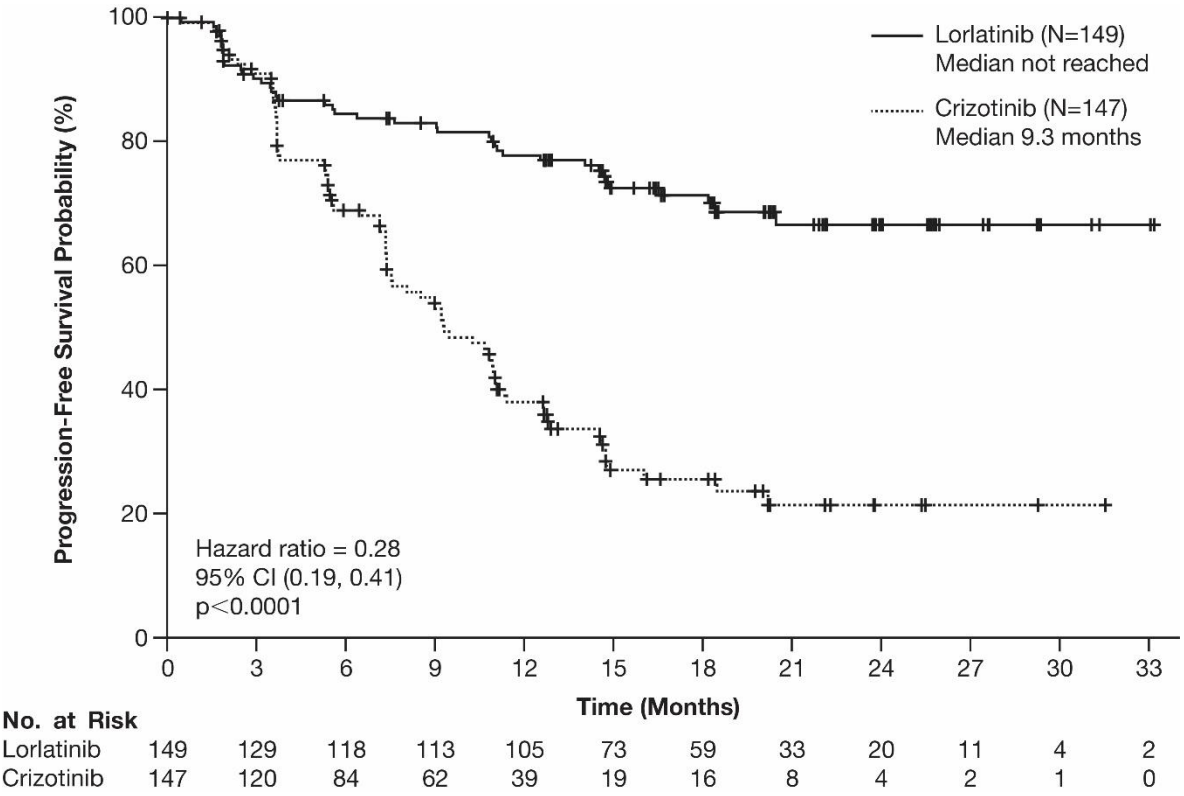
* p-value based on 1-sided stratified log-rank test.

[a] Based on the Brookmeyer and Crowley method.

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

[c] Using exact method based on binomial distribution.

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



Abbreviations: CI=confidence interval; N/No.=number of patients.

The benefit from lorlatinib treatment was comparable across subgroups of baseline patient and disease characteristics, including patients with CNS metastases at baseline (n=38, HR=0.2, 95% CI: 0.10-0.43) and patients without CNS metastases at baseline (n=111, HR=0.32, 95% CI: 0.20-0.49).

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

The use of LORVIQUA in the treatment of ALK-positive advanced NSCLC after treatment with at least one second-generation ALK TKI was investigated in Study A, a single-arm, multicentre Phase 1/2 study and in Study B, a single-arm, multicentre Phase 4 study. In Study A, a total of 139 patients with ALK-positive advanced NSCLC after treatment with at least one second-generation ALK TKI were enrolled in the Phase 2 portion of the study. In Study B, 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 A, the primary efficacy endpoint in the Phase 2 portion of the study was ORR, including intracranial (IC)-ORR, as per Independent Central Review (ICR) according to modified RECIST v1.1. Secondary endpoints included DOR, IC-DOR, time-to-tumour response (TTR) and PFS. In Study B, 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 139 ALK-positive advanced NSCLC patients after treatment with at least one second-generation ALK TKI in Study A were 56% female, 48% White, 38% Asian, and the median age was 53 years (range: 29-83 years) with 16% of patients ≥ 65 years of age. The ECOG performance status at baseline was 0 or 1 in 96% patients. Brain metastases were present at baseline in 67% of patients. Of the 139 patients, 20% received 1 prior ALK TKI, excluding crizotinib, 47% received 2 prior ALK TKIs and 33% 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 B were 42% female, 76% White, 21% Asian, and the median age was 59 years (range: 26-87 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 15% received ceritinib as their prior ALK TKIs.

The main efficacy results for Study A and Study B are included in Tables 4 and 5.

Table 4. Overall efficacy results in Study A and Study B by prior treatment

Efficacy parameter	**One prior ALK TKI[a] with or without prior chemotherapy (N = 99)[b]**	**Two or more prior ALK TKIs with or without prior chemotherapy (N = 111)[c]**
Objective response rate[d]	42.4%	39.6%
(95% CI)	(32.5, 52.8)	(30.5, 49.4)
Complete response, n	5	2
Partial response, n	37	42
Duration of response		
Median, months	NE	9.9
(95% CI)	(7.8, NE)	(5.7, 24.4)
Progression-free survival		
Median, months	8.3	6.9
(95% CI)	(6.3, 16.5)	(5.4, 9.5)

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

[a] Alectinib, brigatinib, or ceritinib.

[b] Pooled efficacy results from Study A and B

[c] Efficacy results from Study A only

[d] Per ICR.

Table 5. Intracranial* efficacy results in Study A and Study B by prior treatment

Efficacy parameter	One prior ALK TKI[a] with or without prior chemotherapy (N = 19)[b]	Two or more prior ALK TKIs with or without prior chemotherapy (N = 48)[c]
Objective response rate[d]	63.2%	52.1%
(95% CI)	(38.4, 83.7)	(37.2, 66.7)
Complete response, n	4	10
Partial response, n	8	15
Duration of intra-cranial response		
Median, months	NE	12.4
(95% CI)	(4.2, NE)	(6.0, NE)

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

* In patients with at least one measurable brain metastasis at baseline.

[a] Alectinib, brigatinib, or ceritinib.

[b] Pooled efficacy results from Study A and B

[c] Efficacy results from Study A only

[d] Per ICR.

In the overall efficacy population of 210 patients, 86 patients had a confirmed objective response by ICR with a median TTR of 1.4 months (range: 1.2 to 16.6 months). The ORR for Asians was 48.5% (95% CI: 36.2, 61.0) and 35.7% for non-Asians (95% CI: 27.4, 44.6). Among the 37 patients with a confirmed IC objective tumour response and at least one measurable brain metastasis at baseline by ICR, the median IC-TTR was 1.4 months (range: 1.2 to 16.2 months). The IC-ORR was 58.3% for Asians (95% CI: 36.6, 77.9) and 47.2% for non-Asians (95% CI: 30.4, 64.5).

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.

After multiple once daily dose administration, 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=53). In a hepatic impairment study following administration of a single oral 100 mg dose of lorlatinib, 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.

No dose adjustments are recommended for patients with mild or moderate hepatic impairment. A reduced dose of lorlatinib is recommended in patients with severe hepatic impairment, i.e. starting dose of 50 mg taken orally once daily (see Section 4.2).

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 contains:

Microcrystalline Cellulose
Dibasic Calcium Phosphate Anhydrous
Sodium Starch Glycolate
Magnesium Stearate

Film-coating contains:

HPMC 2910/Hypromellose
Lactose Monohydrate
Macrogol 4000/PEG 3350
Triacetin
Titanium Dioxide
Ferrosoferric Oxide/Black Iron Oxide
Iron Oxide Red

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please refer to outer carton for expiration date.

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

LORVIQUA 25 mg is supplied in the following package configurations:

- Aluminum foil/Aluminum foil (Alu/Alu) blister foil of 3 blister strips with 10 tablets each.
- Aluminum foil/Aluminum foil (Alu/Alu) blister foil of 6 blister strips with 10 tablets each.
- Aluminum foil/Aluminum foil (Alu/Alu) blister foil of 9 blister strips with 10 tablets each.
- Aluminum foil/Aluminum foil (Alu/Alu) blister foil of 12 blister strips with 10 tablets each.

LORVIQUA 100 mg is supplied in the following package configurations:

- Aluminum foil/Aluminum foil (Alu/Alu) blister foil of 1 blister strip with 10 tablets.
- Aluminum foil/Aluminum foil (Alu/Alu) blister foil of 3 blister strips with 10 tablets each.

Some product strengths or pack sizes may not be available in your country.

6.6 Special Precautions for Disposal and Other Handling

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

7. MANUFACTURER

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1,
79108 Freiburg Im Breisgau, Germany.

Date of Revision: 09 MAR 2026

LORVIQUA-0326