PT. Pfizer Indonesia
Local Product Document

Generic Name: Lorlatinib
Trade Name: LORLAK®
CDS Effective Date: November 11, 2020
Supersedes: September 11, 2020

1. NAME OF THE MEDICINAL PRODUCT

1.1. Product name
LORLAK®

1.2. Strength
25 mg and 100 mg

1.3. Pharmaceutical dosage form
Film-coated tablet

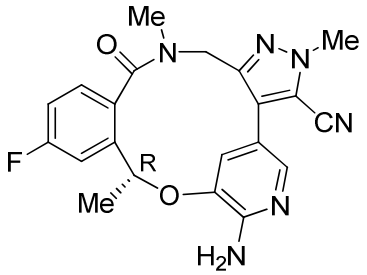
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Structure



3. PHARMACEUTICAL FORM

25 mg: Round light pink film-coated tablet, debossed with “Pfizer” on one side and “25” and“ LLN” on the other side.

100 mg: Oval dark pink film-coated tablet, debossed with “Pfizer” on one side and “LLN 100” on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

LORLAK® is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after previously treated with one or more ALK tyrosine kinase inhibitors (TKIs).

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

ALK-positive status should be established using a validated ALK assay. 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 LORLAK® is 100 mg taken orally once daily continuously. Continue treatment as long as the patient is deriving clinical benefit from therapy.

LORLAK® 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: LORLAK® 75 mg taken orally once daily
- Second dose reduction: LORLAK® 50 mg taken orally once daily

LORLAK® should be permanently discontinued if the patient is unable to tolerate LORLAK® 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 LORLAK® Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	LORLAK® 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 LORLAK® at same dose.
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 LORLAK® at the same dose without interruption.

Table 1. Recommended LORLAK® Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	LORLAK® Dosing
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 LORLAK® until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to moderate or mild severity grade. Re-challenge at same LORLAK® 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 LORLAK® 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 LORLAK® at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue LORLAK®.
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 Grade 2: Moderate	Withhold lorlatinib until symptoms have returned to baseline and consider initiating 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	Permanently discontinue lorlatinib.

Table 1. Recommended LORLAK® Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	LORLAK® Dosing
OR Grade 4: Life-threatening/Urgent intervention indicated	
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. If pacemaker placed, resume lorlatinib at full dose. If no pacemaker placed, resume lorlatinib at

Table 1. Recommended LORLAK® Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	LORLAK® Dosing
	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 lorlatinib until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume lorlatinib at the same dose. If Grade 3 hypertension recurs, withhold lorlatinib 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 lorlatinib.
Grade 4 (Life-threatening consequences, urgent intervention indicated)	Withhold lorlatinib until recovery to Grade 1 or less, and resume at a reduced dose or permanently discontinue lorlatinib. If Grade 4 hypertension recurs, permanently discontinue lorlatinib.
Hyperglycaemia	
Grade 3 OR Grade 4 (Persistent hyperglycaemia greater than 250 mg/dL despite optimal anti-hyperglycaemic therapy)	Withhold lorlatinib until hyperglycaemia is adequately controlled, then resume lorlatinib at the next lower dosage. If adequate hyperglycaemic control cannot be achieved with optimal medical management, permanently discontinue lorlatinib.
Other adverse 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 LORLAK® until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume LORLAK® 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

Table 1. Recommended LORLAK® Dose Modifications for Adverse Drug Reactions

Adverse Drug Reaction	LORLAK® Dosing

(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 LORLAK® 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 LORLAK® 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, LORLAK® 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 hepatic impairment. Limited information is available for lorlatinib in patients with moderate or severe hepatic impairment. Therefore, LORLAK® is not recommended in patients with moderate to severe hepatic impairment (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 LORLAK® 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 LORLAK®. 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 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).

Risk of serious hepatotoxicity with concomitant use of strong CYP3A inducers
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 LORLAK® (see Sections 5.1 and 5.3). Women of childbearing potential should be advised to avoid becoming pregnant while receiving LORLAK®. A highly effective non-hormonal method of contraception is required for female patients during treatment with LORLAK®, 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 LORLAK® 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. Thus, use of a concomitant strong CYP3A inhibitor should be avoided, or an alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered. If use of a concomitant strong CYP3A inhibitor cannot be avoided, a dose reduction of lorlatinib is recommended (see Section 4.2). Note that a dose reduction of lorlatinib may not sufficiently mitigate the risk associated with lorlatinib exposure increase with concomitant strong CYP3A inhibitor use.

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.

CYP2B6 substrates

Lorlatinib 100 mg once daily for 15 days decreased AUC_{inf} and C_{max} of a single oral 100 mg dose of bupropion (a combined CYP2B6 and CYP3A4 substrate) by 25% and 27%, respectively. Thus, lorlatinib is a weak inducer of CYP2B6, and no dose adjustment is necessary when lorlatinib is used in combination with medicinal products that are mainly metabolised by CYP2B6.

CYP2C9 substrates

Lorlatinib 100 mg once daily for 15 days decreased AUC_{inf} and C_{max} of a single oral 500 mg dose of tolbutamide (a sensitive CYP2C9 substrate) by 43% and 15%, respectively. Thus, lorlatinib is a weak inducer of CYP2C9, and no dose adjustment is required for medicinal products that are mainly metabolised by CYP2C9. However, patients should be monitored in case of concomitant treatment with medicinal products with narrow therapeutic indices metabolised by CYP2C9 (e.g., coumarin anticoagulants).

UGT substrates

Lorlatinib 100 mg once daily for 15 days decreased AUC_{inf} and C_{max} of a single oral 500 mg dose of acetaminophen (a UGT, SULT and CYP1A2, 2A6, 2D6, and 3A4 substrate) by 45% and 28%, respectively. Thus, lorlatinib is a weak inducer of UGT, and no dose adjustment is required for medicinal products that are mainly metabolised by UGT. However, patients should be monitored in case of concomitant treatment with medicinal products with narrow therapeutic indices metabolised by UGT.

P-glycoprotein substrates

Lorlatinib 100 mg once daily for 15 days decreased AUC_{inf} and C_{max} of a single oral dose of 60 mg fexofenadine [a sensitive P-glycoprotein (P-gp) substrate] by 67% and 63%, respectively. Thus, lorlatinib is a moderate inducer of P-gp. Medicinal products that are P-gp substrates with narrow therapeutic indices (e.g. digoxin, dabigatran etexilate) should be used with caution in combination with lorlatinib due to the likelihood of reduced plasma concentrations of these substrates.

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, lorlatinib has a low potential to cause drug-drug interactions by induction of CYP1A2. *In vitro*, the major circulating metabolite (M8) of 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 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 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. *In vitro* studies indicated that lorlatinib may have the potential to inhibit BCRP (gastrointestinal tract), OATP1B1, OATP1B3, OCT1, MATE1 and OAT3 at clinically relevant concentrations. Lorlatinib should be used with caution in combination with substrates of BCRP, OATP1B1, OATP1B3, OCT1, MATE1 and OAT3 as clinically relevant changes in the plasma exposure of these substrates cannot be ruled out.

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 LORLAK®. A highly effective nonhormonal method of contraception is required for female patients during treatment with LORLAK®, 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 LORLAK® 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

Based on findings from animal studies and its mechanism of action, lorlatinib can cause embryo-fetal harm when administered to a pregnant woman. There are no data in pregnant women using lorlatinib.

Administration of lorlatinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in embryolethality, abortions and malformations. 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.

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

LORLAK® 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.

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

Fertility

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

Dedicated fertility studies were not conducted with lorlatinib. Effects on male reproductive organs were observed in repeat dose toxicity studies and included lower testicular, epididymal and prostate weights; testicular tubular degeneration/atrophy; prostatic atrophy; and/or epididymal inflammation at 20 mg/kg/day and 7 mg/kg/day in rats and dogs, respectively (approximately 4 and 1.6 times the human clinical exposure at 100 mg based on AUC). The effects on male reproductive organs were fully or partially reversible.

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 LORLAK® in 476 adult patients with ALK-positive or c-ros oncogene 1 (ROS1)-positive metastatic NSCLC who received LORLAK® 100 mg orally once daily in single-arm Study B7461001 or randomized, open label, active controlled Phase 3 Study B7461006.

The median duration of treatment was 16.3 months (range: 0 day to 55 months), the median age was 55 years (range: 19 to 90 years), and 25% of patients were older than 65 years. A total of 57% of patients were female, 50% of patients were White, and 39% of patients were Asian, and 1% were Black.

The most frequently reported adverse drug reactions were hypercholesterolaemia (81.1%), hypertriglyceridaemia (67.2%), oedema (55.7%), peripheral neuropathy (43.7%), weight increased (30.9%), cognitive effects (27.7%), fatigue (27.3%), arthralgia (23.5%), diarrhoea (22.9%), and mood effects (21.0%).

Serious adverse drug reactions were reported in 7.4% 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 20.0% of patients receiving lorlatinib. The most common adverse drug reactions that led to dose reductions were oedema and peripheral neuropathy. Permanent treatment discontinuation associated with adverse drug reactions occurred in 3.2% of patients receiving lorlatinib. The most frequent adverse drug reactions that led to a permanent discontinuation were cognitive effects, peripheral neuropathy, and pneumonitis.

Table 2. Adverse Drug Reactions (ADRs) by System Organ Class (SOC) and Council for International Organizations of Medical Sciences (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC.

It presents ADRs experienced by anaplastic lymphoma kinase (ALK)-positive or c-ros oncogene 1 (ROS1)-positive metastatic non-small cell lung cancer (NSCLC) patients who participated in Study B7461001 (N=327) or Study B7461006 (N=149) and received lorlatinib 100 mg once daily orally (see Section 5.1). ADRs are listed in order of decreasing medical seriousness or clinical importance within each CIOMS frequency category and SOC

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥ 1/1,000 to < 1/100
Blood and lymphatic system disorders	Anaemia		
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] Headache	Speech effects[g]	
Eye disorders	Vision disorder[h]		
Vascular disorders	Hypertension		
Respiratory, thoracic and mediastinal disorders		Pneumonitis[i]	
Gastrointestinal disorders	Diarrhoea Nausea Constipation		
Skin and subcutaneous tissue disorders	Rash		
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia		
General disorders and administration site conditions	Oedema[j] Fatigue[k]		
Investigations	Weight increased Lipase increased Amylase increased		Electrocardiogram PR prolongation

Preferred terms (PTs) are listed according to MedDRA version 23.0.
Date of data cutoff: B7461001: 14May2019; B7461006: 20Mar2020.

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 cutoff date and contributing to the relevant adverse drug reaction are indicated in parentheses, as listed below.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SOC=System Organ Class.

[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 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] 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] Oedema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).
[k] 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 81.1% and 67.2% of patients, respectively. Mild or moderate adverse drug reactions of hypercholesterolaemia or hypertriglyceridaemia occurred in 62.8% and 47.9% of patients, respectively. No patient was discontinued from treatment with lorlatinib due to hypercholesterolaemia or hypertriglyceridaemia (see Sections 4.2 and 4.4). The median time to onset for both hypercholesterolaemia and hypertriglyceridaemia was 15 days. The median duration of hypercholesterolaemia and hypertriglyceridaemia was 451 and 427 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 (27.7%), mood effects (21.0%), 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 (11.3%), and the most frequent Grade 3 or 4 reactions were cognitive disorder and confusional state (0.8% and 1.7%, respectively). The most frequent mood effect of any grade was anxiety (6.5%), and the most frequent Grade 3 or 4 reactions were irritability and depression (0.8% and 0.4%, respectively).

The most frequent speech effect of any grade was dysarthria (4.0%), and the Grade 3 or 4 reactions were dysarthria, slow speech, and speech disorder (0.2% each). The most frequent psychotic effect of any grade was hallucination (2.9%), and the most frequent Grade 3 or 4 reactions were hallucination auditory and hallucination visual (0.2% each). Median time to onset for cognitive, mood, speech, and psychotic effects was 109, 43, 49, and 23 days, respectively. Median duration of cognitive, mood, speech, and psychotic effects was 223, 143, 147, and 78 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, randomized, 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 randomization; whole brain irradiation within 4 weeks prior to randomization.

Patients were randomized 1:1 to receive lorlatinib 100 mg orally once daily or crizotinib 250 mg orally twice daily. Randomization was stratified by ethnic origin (Asian vs. non-Asian) and the presence or absence of CNS metastases at baseline. Treatment on both arms was continued until disease progression or unacceptable toxicity. The major efficacy outcome measure was progression-free survival (PFS) as determined by Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1). Additional efficacy outcome measures were overall survival (OS), 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 randomized 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 (94%) 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 LORLAK® arm over the crizotinib arm. The benefit from lorlatinib treatment was comparable across subgroups of baseline patient and disease characteristics.

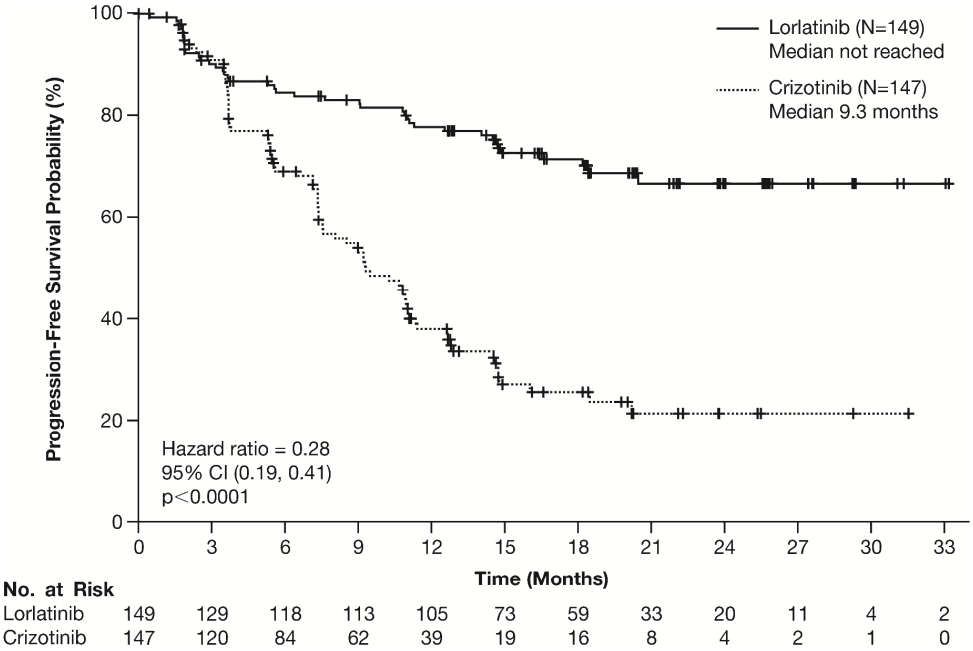
Table 3. Overall Efficacy Results in CROWN Study

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 favor 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. Lorlatinb 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 LORLAK® 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. 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. Patients received LORLAK® orally at the recommended dose of 100 mg once daily, continuously.

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 1.1). Secondary endpoints included DOR, intracranial DOR, time-to-tumor response (TTR), and progression-free survival (PFS).

Patient demographics of the 197 ALK-positive advanced NSCLC patients previously treated with 1 or more ALK TKIs, 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.

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

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

Efficacy Parameter	Group A Crizotinib (N=59)	Group B 1 ALK TKI,[a] excluding crizotinib as the only TKI (N=27)	Group C 2 or more ALK TKIs (N=111)	Pooled Groups A, B, C 1 or more ALK TKIs (N=197)
Objective response rate[b]	69.5%	33.3%	38.7%	47.2%
(95% CI)[c]	(56.1, 80.8)	(16.5, 54.0)	(29.6, 48.5)	(40.1, 54.4)
Complete response, n	1	1	2	4
Partial response, n	40	8	41	89
Duration of response				
Median, months	NR	NR	NR	NR
(95% CI)[d]	(11.1, NR)	(4.1, NR)	(5.5, NR)	(11.1, NR)
Progression-free survival				
Median, months	NR	5.5	6.9	7.4
(95% CI)[d]	(12.5, NR)	(2.9, 9.0)	(5.4, 9.5)	(5.6, 11.0)

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 by Prior Treatment*

Efficacy Parameter	Group A Crizotinib (N=37)	Group B One 2nd generation ALK TKI[a] (N=12)	Group C 2 or more ALK TKIs (N=83)	Pooled Groups A, B, C 1 or more ALK TKIs (N=132)
Objective response rate[b]	67.6%	41.7%	48.2%	53.0%
(95% CI)[c]	(50.2, 82.0)	(15.2, 72.3)	(37.1, 59.4)	(44.2, 61.8)
Complete response, n	10	1	24	35
Partial response, n	15	4	16	35
Duration of response				
Median, Months	NR	NR	14.5	14.5
(95% CI)[d]	(NR, NR)	(4.1, NR)	(8.3, 14.5)	(NR, NR)

* In patients with at least 1 measurable baseline brain metastasis.
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 93 patients with a confirmed objective response by ICR, the median TTR was 1.4 months (range: 1.1 to 11.0 months). Among the 70 patients with a confirmed objective tumor response by ICR, the median intracranial-TTR was 1.4 months (range: 1.1 to 6.2 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.

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=50). No dose adjustments are recommended for patients with mild hepatic impairment (see Section 4.2). Lorlatinib has not been studied in patients with moderate or severe hepatic impairment.

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 LORLAK® 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/Calcium hydrogen phosphate
Sodium starch glycolate
Magnesium stearate

Film-coating contains:

Hydroxypropyl methylcellulose (HPMC) 2910/Hypromellose (E464)
Lactose monohydrate
Macrogol/Polyethylene glycol (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

36 months

6.4. Special precautions for storage

Store below 30°C

6.5. Nature and contents of container

OPA/Al/PVC blisters with aluminium foil backing containing 10 film-coated tablets.

LORLAK® 25 mg film-coated tablets

Each pack contains 10 film-coated tablets in 1 blister.

LORLAK® 100 mg film-coated tablets

Each pack contains 10 film-coated tablets in 1 blister.

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. MARKETING AUTHORISATION HOLDER NAME AND ADDRESS

Manufactured by:
Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Germany

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER

LORLAK® 25 mg Film-coated tablet; Box of 1 blister @ 10 film-coated tablets; No. Reg. DKI2258501717A1
LORLAK® 100 mg Film-coated tablet; Box of 1 blister @ 10 film-coated tablets; No. Reg. DKI2258501717B1

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

12/2022

CDS version 6.0