

Generic Name: Lorlatinib  
Trade Name: LORLAK®  
CDS Effective Date: September 11, 2020  
Supersedes: NA  
Approved by BPOM:

**PT. Pfizer Indonesia  
Local Product Document**

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**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

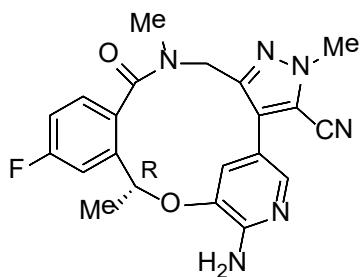
**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

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.

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## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

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

### 4.2. Posology and method of administration

ALK-positive status should be established using a validated ALK assay.

#### 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.

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

Adverse Reaction	LORLAK® Dosing
<b>Hypercholesterolaemia or Hypertriglyceridaemia</b>	
Mild hypercholesterolaemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L)	
<u>OR</u>	
Moderate hypercholesterolaemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L)	Introduce or modify lipid-lowering therapy <sup>a</sup> 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)	
<u>OR</u>	
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)	Introduce the use of lipid-lowering therapy; <sup>a</sup> if currently on lipid-lowering therapy, increase the dose of this therapy <sup>a</sup> in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue LORLAK® at the same dose without interruption.
<u>OR</u>	
Severe hypertriglyceridaemia (triglycerides between 501 and 1000 mg/dL or 5.71 and 11.4 mmol/L)	

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

Adverse Reaction	LORLAK® Dosing
Life-threatening hypercholesterolaemia (cholesterol over 500 mg/dL or over 12.92 mmol/L)  <u>OR</u>  Life-threatening hypertriglyceridaemia (triglycerides over 1000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy <sup>a</sup> or increase the dose of this therapy <sup>a</sup> 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 <sup>a</sup> in accordance with respective prescribing information.  If severe hypercholesterolaemia and/or hypertriglyceridaemia recur(s) despite maximal lipid-lowering therapy <sup>a</sup> in accordance with respective prescribing information, reduce LORLAK® by 1 dose level.
<b>Central nervous system effects<sup>b,c</sup></b>	
Grade 2: Moderate  <u>OR</u>  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®.
<b>Lipase/Amylase increase</b>	
Grade 3: Severe  <u>OR</u>  Grade 4: Life-threatening/Urgent intervention indicated	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at 1 reduced dose level.
<b>Pneumonitis</b>	
Grade 1: Mild  <u>OR</u>  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.

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

<b>Adverse Reaction</b>	<b>LORLAK® Dosing</b>
<u>OR</u>	
Grade 4: Life-threatening/Urgent intervention indicated	
<b>PR interval prolongation/Atrioventricular (AV) block</b>	
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

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Adverse Reaction	LORLAK® Dosing
	1 reduced dose level only when symptoms resolve and PR interval is less than 200 msec.
<b>Hypertension</b>	
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)	<p>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.</p> <p>If Grade 3 hypertension recurs, withhold lorlatinib until recovery to Grade 1 or less, and resume at a reduced dose.</p> <p>If adequate hypertension control cannot be achieved with optimal medical management, permanently discontinue lorlatinib.</p>
Grade 4 (Life-threatening consequences, urgent intervention indicated)	<p>Withhold lorlatinib until recovery to Grade 1 or less, and resume at a reduced dose or permanently discontinue lorlatinib.</p> <p>If Grade 4 hypertension recurs, permanently discontinue lorlatinib.</p>
<b>Hyperglycaemia</b>	
Grade 3 <u>OR</u> Grade 4 (Persistent hyperglycaemia greater than 250 mg/dL despite optimal anti-hyperglycaemic therapy)	<p>Withhold lorlatinib until hyperglycaemia is adequately controlled, then resume lorlatinib at the next lower dosage.</p> <p>If adequate hyperglycaemic control cannot be achieved with optimal medical management, permanently discontinue lorlatinib.</p>
<b>Other adverse reactions<sup>c</sup></b>	
Grade 1 <u>OR</u> 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; ECG=electrocardiogram; HMG CoA=3-hydroxy-3-methylglutaryl coenzyme A; ULN=upper limit of normal.

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

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

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

Adverse Reaction	LORLAK® Dosing
° 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):  $\geq 30$  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 ( $\geq 65$  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).

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#### **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 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

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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.

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### 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<sub>2</sub>-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<sub>inf</sub> ratio, expressed as a percentage: 97.6%, 104.3%). No dose adjustment is required when lorlatinib is taken with proton-pump inhibitors, H<sub>2</sub>-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<sub>inf</sub> 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

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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.

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*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.

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#### **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.

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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**

The data described below reflect exposure to LORLAK® in 295 adult patients with ALK-positive or c-ros oncogene 1 (ROS1)-positive metastatic NSCLC who received LORLAK® 100 mg orally once daily in Study B7461001.

The median duration of treatment was 16.3 months (range: 1 day to 39.7 months), the median age was 53 years (range: 19 to 85 years), and 18% of patients were older than 65 years. A total of 58% of patients were female, 49% of patients were White, and 37% of patients were Asian.

The most frequently reported adverse reactions were hypercholesterolaemia (84.4%), hypertriglyceridaemia (67.1%), oedema (54.6%), peripheral neuropathy (47.8%), cognitive effects (28.8%), fatigue (28.1%), weight increased (26.4%), arthralgia (24.7%), mood effects (22.7%), and diarrhoea (22.7%).

Dose reductions due to adverse reactions occurred in 23.4% of patients receiving lorlatinib. The most common adverse reactions that led to dose reductions were oedema and peripheral neuropathy. Permanent treatment discontinuation associated with adverse reactions occurred in 3.1% of patients receiving lorlatinib. The most frequent adverse reactions that led to a permanent discontinuation were cognitive effects and psychotic effects.

Serious adverse reactions were reported in 7.8% of patients receiving lorlatinib. The most frequent serious adverse reactions reported were cognitive effects 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.**

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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 and received lorlatinib 100 mg once daily orally (N=295) (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 <sup>a</sup> Hypertriglyceridaemia <sup>b</sup>	Hyperglycaemia*	
Psychiatric disorders	Mood effects <sup>c</sup>	Psychotic effects <sup>d</sup> Mental status changes	
Nervous system disorders	Cognitive effects <sup>e</sup> Peripheral neuropathy <sup>f</sup> Headache	Speech effects <sup>g</sup>	
Eye disorders	Vision disorder <sup>h</sup>		
Vascular disorders	Hypertension*		
Respiratory, thoracic and mediastinal disorders		Pneumonitis <sup>i</sup>	
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 <sup>j</sup> Fatigue <sup>k</sup>		
Investigations	Weight increased Lipase increased Amylase increased		Electrocardiogram PR prolongation

Preferred terms (PTs) are listed according to MedDRA version 20.1.

Date of data cutoff: 02-Feb-2018.

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 reaction are indicated in parentheses, as listed below.

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SOC=System Organ Class.

\* Based on data from 476 patients who received lorlatinib 100 mg once daily in Study A and CROWN.

<sup>a</sup> Hypercholesterolaemia (including blood cholesterol increased, hypercholesterolaemia).

<sup>b</sup> Hypertriglyceridaemia (including blood triglycerides increased, hypertriglyceridaemia).

<sup>c</sup> Mood effects (including affective disorder, affect lability, aggression, agitation, anxiety, depressed mood,

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depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress).

<sup>d</sup> Psychotic effects (including hallucination, hallucination auditory, hallucination visual).

<sup>e</sup> 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.

<sup>f</sup> Peripheral neuropathy (including burning sensation, carpal tunnel syndrome, dysaesthesia, formication, gait disturbance, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral sensory neuropathy, peroneal nerve palsy, sensory disturbance).

<sup>g</sup> Speech effects (including dysarthria, slow speech, speech disorder).

<sup>h</sup> Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).

<sup>i</sup> Pneumonitis (including interstitial lung disease, pneumonitis).

<sup>j</sup> Oedema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).

<sup>k</sup> Fatigue (including asthenia, fatigue).

### Description of selected adverse reactions

#### *Hypercholesterolaemia/Hypertriglyceridaemia*

In Study B7461001, adverse reactions of increase in serum cholesterol or triglycerides were reported in 84.4% and 67.1% of patients, respectively. Mild or moderate adverse reactions of hypercholesterolaemia or hypertriglyceridaemia occurred in 67.8% and 50.5% 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 381 and 405 days, respectively.

#### *Central nervous system effects*

In Study B7461001, CNS adverse reactions were primarily cognitive effects (28.8%), mood effects (22.7%), speech effects (9.8%), and psychotic effects (7.8%), and were generally mild, transient, and reversible upon dose delay and/or dose reduction (see Sections 4.2 and 4.4). The most common cognitive effect of any grade was memory impairment (11.5%), and the most common Grade 3 or 4 reactions were cognitive disorder and confusional state (0.7% each). The most common mood effect of any grade was irritability (6.1%), which was also the most common Grade 3 or 4 reaction (1.0%). The most common speech effect of any grade was dysarthria (4.1%), and the most common Grade 3 or 4 reaction was slow speech (0.3%). The most common psychotic effect of any grade was hallucination (3.7%) and the most common Grade 3 or 4 reactions were hallucination, hallucination auditory, and hallucination visual (0.3% each). Median time to onset for cognitive, mood, speech, and psychotic effects was 92, 44, 42, and 23 days, respectively. Median duration of cognitive, mood, speech, and psychotic effects was 224, 83, 106, and 74 days, respectively.

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## 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<sup>L1196M</sup> 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

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 objective response rate (ORR), including intracranial ORR, as per Independent Central Review (ICR) according to modified Response Evaluation Criteria in Solid Tumors (modified RECIST version 1.1). Secondary endpoints included duration of response (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%  $\geq$ 65 years of age. The Eastern Cooperative Oncology

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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 3 and 4.

**Table 3. Efficacy Results in Study B7461001 by Prior ALK TKI Treatment**

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

<sup>a</sup> Alectinib, brigatinib, or ceritinib.

<sup>b</sup> Per ICR.

<sup>c</sup> Using exact method based on binomial distribution.

<sup>d</sup> Using the Brookmeyer Crowley method.

**Table 4. Intracranial Efficacy Results in Study B7461001 by Prior Treatment\***

Efficacy Parameter	Group A	Group B	Group C	Pooled Groups A, B, C
	Crizotinib (N=37)	One 2 <sup>nd</sup> generation ALK TKI <sup>a</sup> (N=12)	2 or more ALK TKIs (N=83)	1 or more ALK TKIs (N=132)
Objective response rate <sup>b</sup> (95% CI) <sup>c</sup>	67.6% (50.2, 82.0)	41.7% (15.2, 72.3)	48.2% (37.1, 59.4)	53.0% (44.2, 61.8)
Complete response, n	10	1	24	35
Partial response, n	15	4	16	35
Duration of response				
Median, Months (95% CI) <sup>d</sup>	NR (NR, NR)	NR (4.1, NR)	14.5 (8.3, 14.5)	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; ORR=objective response rate; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

<sup>a</sup> Alectinib, brigatinib, or ceritinib.

<sup>b</sup> Per ICR.

<sup>c</sup> Using exact method based on binomial distribution.

<sup>d</sup> Using the Brookmeyer Crowley method.

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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<sub>2</sub>-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  $\alpha_1$ -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

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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  $\geq$ 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  $>2.5 \times$  ULN, or if due to underlying malignancy,  $>5.0 \times$  ULN or with total bilirubin  $>1.5 \times$  ULN. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild hepatic impairment (n=50). No dose

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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  $>1.5 \times \text{ULN}$  or estimated  $\text{CL}_{\text{cr}} < 60 \text{ mL/min}$ . 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 ( $\text{CL}_{\text{cr}} \geq 30 \text{ mL/min}$ ). 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  $\text{mL/min}/1.73 \text{ m}^2$ )  $\times$  measured body surface area/ $1.73 \geq 30 \text{ mL/min}$ ]. In this study, lorlatinib  $\text{AUC}_{\text{inf}}$  increased by 41% in subjects with severe renal impairment (absolute eGFR  $< 30 \text{ mL/min}$ ) compared to subjects with normal renal function (absolute eGFR  $\geq 90 \text{ mL/min}$ ). 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 ( $\geq 65$ years)*

Of the 295 patients in safety population in Study B7461001, 18.3% 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. Although data are limited, no clinically relevant differences in safety or efficacy were observed between patients aged greater than or equal to 65 years 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 central nervous system (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  $\text{C}_{\text{max}}$ ). All target organ findings with the exception of the hepatic bile duct hyperplasia (approximately 7.1 to

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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 embryo lethality, 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)  
Ferrosferric oxide/Iron oxide black (E172)  
Iron oxide red (E172)

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## **6.2. Incompatibilities**

Not applicable

## **6.3. Shelf life**

36 months

## **6.4. Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **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. DKI  
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**HARUS DENGAN RESEP DOKTER**

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

02/2022

CDS version 5.0