SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lorviqua 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg of lorlatinib.

Excipient with known effect
Each film-coated tablet contains 1.58 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Round (8 mm) light pink immediate release film-coated tablet, debossed with "Pfizer" on one side and "25" and "LLN" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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.

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.

Posology

The recommended dose is 100 mg lorlatinib taken orally once daily.

Duration of treatment
Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity.

Delayed or missed doses
If a dose of Lorviqua 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 or dose reduction may be required based on individual safety and tolerability. Lorlatinib dose reduction levels are summarised below:

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

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

Dose modification recommendations for toxicities and for patients who develop atrioventricular (AV) block are provided in Table 1.

Table 1. Recommended lorlatinib dose modifications for adverse reactions

Adverse reaction[a]	**Lorlatinib 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) OR 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)	Introduce or modify lipid-lowering therapy[b] in accordance with respective prescribing information; continue lorlatinib at same dose.

Table 1. Recommended lorlatinib dose modifications for adverse reactions

Adverse reaction[a]	**Lorlatinib dosing**
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 1,000 mg/dL or 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[b]; if currently on lipid-lowering therapy, increase the dose of this therapy[b] in accordance with respective prescribing information; or change to a new lipid-lowering therapy[b]. Continue lorlatinib at the same dose without interruption.
Life-threatening hypercholesterolaemia (cholesterol over 500 mg/dL or over 12.92 mmol/L) OR Life-threatening hypertriglyceridaemia (triglycerides over 1,000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[b] or increase the dose of this therapy[b] in accordance with respective prescribing information or change to a new lipid-lowering therapy[b]. Withhold lorlatinib until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to moderate or mild severity grade. Re-challenge at same lorlatinib dose while maximising lipid-lowering therapy[b] in accordance with respective prescribing information. If severe hypercholesterolaemia and/or hypertriglyceridaemia recur despite maximal lipid-lowering therapy[b] in accordance with respective prescribing information, reduce lorlatinib by 1 dose level.
Central nervous system (CNS) effects (comprises psychotic effects and changes in cognition, mood, mental state or speech)	
Grade 2: Moderate OR Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume lorlatinib at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.
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.
Interstitial lung disease (ILD)/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 lorlatinib dose modifications for adverse reactions

Adverse reaction[a]	**Lorlatinib 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 AV 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 AV 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 1 reduced dose level only when symptoms resolve, and PR interval is less than 200 msec.

Table 1. Recommended lorlatinib dose modifications for adverse reactions

Adverse reaction[a]	Lorlatinib dosing
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 (greater than 250 mg/dL despite optimal anti-hyperglycaemic therapy) OR Grade 4	Withhold lorlatinib until hyperglycaemia is adequately controlled, then resume lorlatinib at the next lower dose. If adequate hyperglycaemic control cannot be achieved with optimal medical management, permanently discontinue lorlatinib.
Other adverse reactions	
Grade 1: Mild OR Grade 2: Moderate	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3: Severe	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib 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; NCI=National Cancer Institute; SBP=systolic blood pressure; ULN=upper limit of normal.

[a] Grade categories are based on NCI CTCAE classifications.

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

Strong cytochrome P-450 (CYP) 3A4/5 inhibitors

Concurrent use of lorlatinib with medicinal products that are strong CYP3A4/5 inhibitors and grapefruit juice products may increase lorlatinib plasma concentrations. An alternative concomitant medicinal product with less potential to inhibit CYP3A4/5 should be considered (see section 4.5). If a strong CYP3A4/5 inhibitor must be co-administered, the starting lorlatinib dose of 100 mg once daily should be reduced to once daily 75 mg dose (see sections 4.5 and 5.2). If concurrent use of the strong CYP3A4/5 inhibitor is discontinued, lorlatinib should be resumed at the dose used prior to the

initiation of the strong CYP3A4/5 inhibitor and after a washout period of 3 to 5 half-lives of the strong CYP3A4/5 inhibitor.

Special populations

Elderly (≥ 65 years)
Due to the limited data on this population, no dose recommendation can be made for patients aged 65 years and older (see section 5.2).

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

Hepatic impairment
No dose adjustments are recommended for patients with mild hepatic impairment. No information is available for lorlatinib in patients with moderate or severe hepatic impairment. Therefore, lorlatinib is not recommended in patients with moderate to severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of lorlatinib in paediatric patients below 18 years have not been established. No data are available.

Method of administration

Lorviqua is for oral use.

Patients should be encouraged to take their dose of lorlatinib at approximately the same time each day with or without food (see section 5.2). The 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.

4.3 Contraindications

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

Concomitant use of strong CYP3A4/5 inducers (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Hyperlipidaemia

The use of lorlatinib has been associated with increases in serum cholesterol and triglycerides (see section 4.8). Serum cholesterol and triglycerides should be monitored before initiation of lorlatinib; 2, 4 and 8 weeks after initiating lorlatinib; and regularly thereafter. Initiate or increase the dose of lipid-lowering medicinal products, if indicated (see section 4.2).

Central nervous system effects

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

Atrioventricular block

Lorlatinib was studied in a population of patients that excluded those with second-degree or third-degree AV block (unless paced) or any AV block with PR interval > 220 msec. PR interval prolongation and AV block have been reported in patients receiving lorlatinib (see section 5.2). Monitor electrocardiogram (ECG) prior to initiating lorlatinib and monthly thereafter, particularly in patients with predisposing conditions to the occurrence of clinically significant cardiac events. Dose modification may be required for those patients who develop AV block (see section 4.2).

Left ventricular ejection fraction decrease

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

Elevation of pancreatic enzymes

Elevations of lipase and/or amylase have occurred in patients receiving lorlatinib (see section 4.8). Lorlatinib was studied in a population of patients that excluded, at the discretion of the investigator, those with risk factors for pancreatitis, such as uncontrolled hyperglycaemia or gallstone disease. 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).

Interstitial lung disease/Pneumonitis

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

Visual disturbance

Visual disturbance adverse reactions have occurred in patients treated with lorlatinib (see section 4.8). Patients should be advised to report any visual symptoms. For new or worsening severe visual symptoms, an ophthalmologic evaluation and dose reduction should be considered (see section 4.2).

Hypertension

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

Hyperglycaemia

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

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 CYP3A4/5 inducer, was associated with increases of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with no increase of total bilirubin and alkaline phosphatase (see section 4.5). Concomitant use of a strong CYP3A4/5 inducer is contraindicated and should be discontinued 3 plasma half-lives prior to initiating lorlatinib (see sections 4.3 and 4.5).

Other Drug - drug interactions

Concomitant use of moderate CYP3A inducers
No clinically meaningful changes in liver function tests were seen in healthy subjects after receiving a combination of lorlatinib with the moderate CYP3A4/5 inducer modafinil (see section 4.5).

Concomitant use of strong CYP3A inhibitors
Concomitant use with strong CYP3A inhibitors should be avoided (see section 4.5).

CYP3A4/5 substrates
Concurrent administration of lorlatinib with CYP3A4/5 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus and tacrolimus, should be avoided since the concentration of these medicinal products may be reduced by lorlatinib (see section 4.5).

Fertility and pregnancy

Lorlatinib may cause foetal harm. During treatment with lorlatinib and for at least 14 weeks after the final dose, male patients with female partners of childbearing 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. Women of childbearing potential should be advised to avoid becoming pregnant while receiving lorlatinib. A highly effective non-hormonal method of contraception is required for female patients during treatment with lorlatinib, 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 35 days after completing therapy (see section 4.6). It is not known whether lorlatinib affects female fertility.

Lactose intolerance

This medicinal product contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Dietary sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 25 mg or 100 mg tablet. Patients on low sodium diets should be informed that this product is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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

Effect of medicinal products on lorlatinib

Strong CYP3A4/5 inducers

Rifampin, a strong inducer of CYP3A4/5, administered at oral doses of 600 mg once daily for 12 days, reduced the mean lorlatinib area under curve (AUC_{inf}) by 85% and C_{max} by 76% of a single 100 mg oral dose of lorlatinib in healthy volunteers; increases in AST and ALT were also observed. Concomitant administration of lorlatinib with strong CYP3A4/5 inducers (e.g. rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's wort) may decrease lorlatinib plasma concentrations. The use of a strong CYP3A4/5 inducer with lorlatinib is contraindicated (see sections 4.3 and 4.4).

Moderate CYP3A4/5 inducers

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 CYP3A4/5 inducer, modafinil (400 mg once daily for 19 days) in healthy volunteers. Concomitant use of modafinil reduced lorlatinib AUC_{inf} by 23% which is not expected to influence the efficacy of lorlatinib.

CYP3A4/5 inhibitors

Itraconazole, a strong inhibitor of CYP3A4/5, administered at oral doses of 200 mg once daily for 5 days, increased the mean lorlatinib AUC_{inf} by 42% and C_{max} by 24% of a single 100 mg oral dose of lorlatinib in healthy volunteers.

Concomitant administration of lorlatinib with strong CYP3A4/5 inhibitors (e.g. boceprevir, cobicistat, itraconazole, ketoconazole, posaconazole, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either elvitegravir, indinavir, lopinavir or tipranavir) may increase lorlatinib plasma concentrations. Grapefruit products may also increase lorlatinib plasma concentrations and should be avoided. An alternative concomitant medicinal product with less potential to inhibit CYP3A4/5 should be considered.
If a strong CYP3A4/5 inhibitor must be concomitantly administered, a dose reduction of lorlatinib is recommended (see section 4.2).

Effect of lorlatinib on other medicinal products

CYP3A4/5 substrates

In vitro studies indicated that lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A4/5. Lorlatinib 150 mg orally once daily for 15 days decreased AUC_{inf} and C_{max} of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate) by 61% by 50%, respectively; hence, lorlatinib is a moderate CYP3A inducer. Thus, concurrent administration of lorlatinib with CYP3A4/5 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus and tacrolimus, should be avoided since the concentration of these medicinal products may be reduced by lorlatinib (see section 4.4).

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 mgfexofenadine [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 inhibition and induction studies of other CYP enzymes

In vitro, lorlatinib has a low potential to cause drug-drug interactions by induction of CYP1A2.

In vitro studies with drug transporters other than P-gp

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving lorlatinib. A highly effective non-hormonal method of contraception is required for female patients during treatment with lorlatinib, 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 35 days after completing therapy.

During treatment with lorlatinib and for at least 14 weeks after the final dose, male patients with female partners of childbearing potential must use effective contraception, including a condom, and male patients with pregnant partners must use condoms.

Pregnancy

Studies in animals have shown embryo-foetal toxicity (see section 5.3). There are no data from the use of lorlatinib in pregnant women. Lorlatinib may cause foetal harm when administered to a pregnant woman.

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

Breast-feeding

It is unknown whether lorlatinib and its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Lorlatinib should not be used during breast-feeding. Breast-feeding should be discontinued during treatment with lorlatinib and for 7 days after the final dose.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The frequencies of adverse reactions are based on all-cause adverse events.

The most frequently reported adverse reactions (≥20%) in patients treated with lorlatinib at the recommended dosing regimen were hypercholesterolaemia (79.0%), hypertriglyceridaemia (67.5%), oedema (55.4%), peripheral neuropathy (44.2%), fatigue (30.7%), weight gain (29.8%), arthralgia (27.8%), cognitive effects (27.4%), dyspnoea (27.4%), diarrhoea (22.7%) and mood effects (21.4%).

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

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

Tabulated list of adverse reactions

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

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

Table 2. Adverse reactions

System organ class and adverse reaction	Frequency category	All Grades %	Grades 3-4 %
Blood and lymphatic system disorders			
Anaemia	Very common	19.6	4.4
Metabolism and nutrition disorders			
Hypercholesterolaemia[a]	Very common	79.0	19.2
Hypertriglyceridaemia[b]	Very common	67.5	20.3
Hyperglycaemia	Common	9.7	3.7
Psychiatric disorders			
Mood effects[c]	Very common	21.4	1.3
Sleep effects	Very common	10.8	0.4
Psychotic effects[d]	Common	6.9	0.9
Mental status changes	Common	1.1	0.9
Nervous system disorders			
Cognitive effects[e]	Very common	27.4	3.5
Peripheral neuropathy[f]	Very common	44.2	2.6
Headache	Very common	18.6	0.7
Speech effects[g]	Common	8.2	0.7
Eye disorders			
Vision disorder[h]	Very common	16.1	0.2
Vascular disorders			
Hypertension	Very common	14.8	6.0
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea	Very common	27.4	5.7
Cough	Very common	21.0	0
Pneumonitis[i]	Common	2.4	0.7
Gastrointestinal disorders			
Diarrhoea	Very common	22.7	1.8
Nausea	Very common	17.6	0.9
Constipation	Very common	16.8	0.2
Vomiting	Very common	14.1	1.1
Lipase increased	Very common	12.8	6.8
Amylase increased	Very common	11.3	2.7
Pancreatitis	Uncommon	0.5	0.2
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	14.6	2.0
Aspartate aminotransferase increased	Very common	13.9	1.5
Gamma-glutamyl peptidase increased	Common	5.9	2.4
Skin and subcutaneous tissue disorders			
Rash[j]	Very common	14.6	0.2
Renal and urinary disorders			
Proteinuria	Common	3.7	0.4
Musculoskeletal and connective tissue disorders			
Arthralgia	Very common	27.8	0.7
Myalgia[k]	Very common	15.0	0
Blood creatine phosphokinase increased	Common	7.3	1.3
General disorders and administration site conditions			
Oedema[l]	Very common	55.4	2.9
Fatigue[m]	Very common	30.7	1.1
Dizziness	Very common	15.2	0.7
Investigations			
Weight increased	Very common	29.8	11
Atrioventricular block	Common	0.4	0

Adverse reactions that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. Terms actually reported in the studies and contributing to the relevant adverse reaction are indicated in parentheses, as listed below.

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

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

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

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

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

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

[h] Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).
[i] Pneumonitis (including interstitial lung disease, lung opacity, pneumonitis).
[j] Rash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash).
[k] Myalgia (including musculoskeletal pain, myalgia).
[l] Oedema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).
[m] Fatigue (including asthenia, fatigue).

Description of selected adverse reactions

Hypercholesterolaemia/hypertriglyceridaemia
Adverse reactions of increase in serum cholesterol or triglycerides were reported in 79.0% and 67.5% of patients, respectively. Grade 3 or 4 reactions of hypercholesterolaemia and hypertriglyceridaemia were reported in 11.5% and 18.1% of patients, respectively. The median time to onset for hypercholesterolaemia and hypertriglyceridaemia was 15 days (range: 1 to 1921 days) and 16 days (range: 1 to 1921 days), respectively. Median time of occurrence of grade 4 increase in serum cholesterol and triglycerides is 104 days (range: 29 to 518 days) and 120 days (range: 15 to 780 days), respectively. The median duration of hypercholesterolaemia and hypertriglyceridaemia was 526 and 519 days, respectively. Dose interruption due to hypercholesterolaemia and hypertriglyceridaemia occurred in 3.8% and 6.9% of patients, respectively. Dose reduction due to hypercholesterolaemia and hypertriglyceridaemia occurred in 1.3% and 2.7% of patients, respectively.

Central nervous system effects
CNS adverse reactions were primarily cognitive effects (27.4%), mood effects (21.4%), speech effects (8.2%) and psychotic effects (6.9%) (see sections 4.2 and 4.4). The most frequent cognitive effect was memory impairment (10.8%), and the most frequent Grade 3 or 4 reactions were confusional state and cognitive disorder (1.6% and 0.7% respectively). The most frequent mood effect was anxiety (7.3%), and the most frequent Grade 3 and 4 reactions were irritability (0.7%), depression (0.4%), anxiety, agitation and bipolar I disorder (0.2% each). The most frequent speech effect was dysarthria (3.8%), and the Grade 3 or 4 reactions were dysarthria (0.4%), slow speech and speech disorder (0.2% each). The most frequent psychotic effect was hallucination (2.7%) and the most frequent Grade 3 or 4 reactions were hallucination auditory and hallucination visual, delusion, acute psychosis and schizophrenic disorder (0.2% each). Median time to onset for cognitive, mood, speech and psychotic effects was 129, 57, 58 and 27 days, respectively. Median duration of cognitive, mood, speech and psychotic effects was 270, 145, 147 and 83.5 days, respectively. Dose interruption and dose reduction due to CNS adverse reactions occurred in 9.2% and 7.6% of patients, respectively. Permanent discontinuation due to CNS adverse reactions occurred in 1.9% of patients.

Elevation of pancreatic enzymes
Lipase and amylase increased were reported in 12.8% and 11.3% of patients. Grade 3 or 4 reactions of lipase and amylase increased were reported in 6.8% and 2.7%, respectively. Median time of onset of lipase and amylase increased were 141 days and 138 days, respectively. Median duration of these events was 28 and 71 days, respectively. Dose interruption due to lipase increased and amylase increased occurred in 3.4% and 2.1% of patients, respectively. Dose reduction due to lipase increased and amylase increased occurred in 0.8% and 0.4%, respectively.

Peripheral neuropathy
Adverse reactions of peripheral neuropathy were reported in 44.2% of patients. Grade 3 or 4 reactions of peripheral neuropathy were reported in 2.6% of patients. Median time to onset and duration of peripheral neuropathy were 85 days and 306 days, respectively. Dose interruption and dose reduction due to peripheral neuropathy occurred in 4% and 4.6% of

patients, respectively. Permanent discontinuation due to peripheral neuropathy occurred in 0.6% of patients.

Hypertension
Hypertension was reported in 14.8% of patients. Grade 3 or 4 reactions were reported in in 6.0% of patients. Median time to onset and duration of hypertension were 295 days and 505 days, respectively. Dose interruption due to hypertension occurred in 2.1% of patients.

Hyperglycaemia
Hyperglycaemia was reported in 9.7% of patients. Grade 3 or 4 reactions were reported in 3.7% of patients. Median time to onset and duration of hyperglycaemia were 148 days and 118 days, respectively. Dose interruption occurred in 0.8% of patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple
App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Lorlatinib is a selective, adenosine triphosphate (ATP)-competitive inhibitor of ALK and c-ros oncogene 1 (ROS1) tyrosine kinases.
In non-clinical studies, lorlatinib inhibited catalytic activities of non-mutated ALK and clinically relevant ALK mutant kinases in recombinant enzyme and cell-based assays. Lorlatinib demonstrated marked antitumour activity in mice bearing tumour xenografts that express echinoderm microtubule-associated protein-like 4 (EML4) fusions with ALK variant 1 (v1), including ALK mutations L1196M, G1269A, G1202R, and I1171T. Two of these ALK mutants, G1202R and I1171T, are known to confer resistance to alectinib, brigatinib, ceritinib, and crizotinib. Lorlatinib was also capable of penetrating the blood-brain barrier.

Lorlatinib demonstrated activity in mice bearing orthotopic EML4-ALK or EML4-ALK^{L1196M} brain tumour implants.

Clinical efficacy

Previously untreated ALK-positive advanced NSCLC (CROWN Study)

The efficacy of lorlatinib for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicentre Study B7461006 (CROWN study). Patients were required to have 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 stereotactic or partial brain irradiation at least 2 weeks or whole brain irradiation at least 4 weeks prior to randomization. Patients with severe acute or chronic psychiatric conditions, including recent (within the past year) or active suicidal ideation or behaviour, were excluded.

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 Tumours (RECIST) version 1.1 (v1.1). Additional efficacy outcome measures were overall survival (OS) and tumour assessment related endpoints by BICR, including objective response rate (ORR), duration of response (DOR) and time to intracranial progression (IC-TTP). 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) 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. Most patients had adenocarcinoma (95%) and never smoked (59%). The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 or 1 in 96% of patients. CNS metastases as determined by BICR neuroradiologists were present in 26% (n=78) of patients: of these, 30 patients had measurable CNS lesions.

Efficacy results from the CROWN study as assessed by BICR are summarized in Table 3 and Figure 1. Results demonstrated a significant improvement in PFS for the lorlatinib arm over the crizotinib arm. At the data cut-off point (20 March 2020), OS data were not mature.

Table 3. Efficacy results in CROWN study (B7461006)

Efficacy Parameter	**Lorlatinib N=149**	**Crizotinib N=147**
Primary efficacy parameter		
Duration of follow-up		

Median, months (95% CI)[a]	18 (16, 20)	15 (13, 18)
Progression-free survival		
Number of events, n (%)	41 (27.5%)	86 (58.5%)
Progressive disease, n (%)[§]	32 (21.5%)	82 (55.8%)
Death, n (%)	9 (6.0%)	4 (2.7%)
Median, months (95% CI)[a]	NE (NE, NE)	9.3 (7.6, 11.1)
Hazard ratio (95% CI)[b]	0.28 (0.19, 0.41)	
p-value[*]	<0.0001	
Secondary efficacy parameters		
Overall survival		
Number of patients with event, n (%)	23 (15%)	28 (19%)
Median, months (95% CI)[a]	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[b]	0.72 (0.41, 1.25)	
Overall response rate		
Overall response rate n (%) 95% CI[c]	113 (75.8%) 68.2, 82.5	85 (57.8%) 49.4, 65.9
p-value[**]	0.0010	
Complete response	4 (2.7%)	0 (0%)
Partial response	109 (73.2%)	85 (57.8%)
Duration of response		
Number of responders, n	113	85
Median, months (95% CI)[a]	NE (NE, NE)	11 (9.0, 12.9)
Response duration ≥6 months, n (%)	101 (89.4%)	53 (62.4%)
Response duration ≥12 months, n (%)	79 (69.9%)	23 (27.1)%
Response duration ≥18 months, n (%)	34 (30.1%)	9 (10.6%)

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

[*] p-value based on 2-sided stratified log-rank test.

[**] p-value based on 2-sided Cochran-Mantel-Haenszel test.

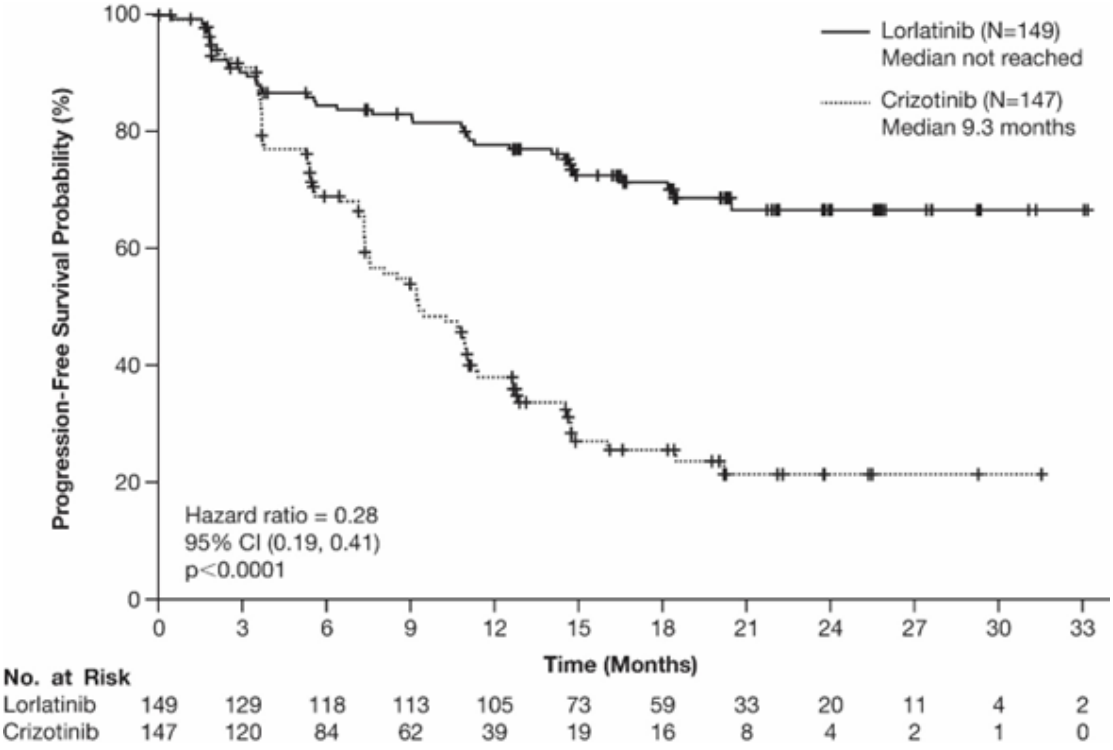
[§] Results from the pre-specified sensitivity analysis that includes events after new anti-cancer treatment and after 2 or more missed assessments for the sensitivity analysis were consistent with the primary analysis of PFS by BICR.

[a] Based on the Brookmeyer and Crowley method.

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

[c] Using exact method based on binomial distribution.

Figure 1. Kaplan-Meier plot of progression-free survival by blinded independent central review in CROWN study (B7461006)



The time to intracranial progression (IC-TTP) was longer with lorlatinib than with crizotinib (HR: 0.07; 95% CI: 0.03, 0.17). The median (95% CI) IC-TTP was not estimable in the lorlatinib arm and 16.6 months (11.1, NE) in the crizotinib arm.

The results of prespecified exploratory analyses of intracranial response rate in 30 patients with measurable CNS lesions at baseline and 78 patients with measurable or non-measurable CNS lesions at baseline as assessed by BICR are summarized in Table 4. No patients with measurable CNS lesions at baseline received prior brain radiation. For patients with non-measurable CNS lesions only at baseline 35.4% (17/48) received prior brain radiation within 6 months of randomisation.

Table 4. Intracranial responses in patients with intracranial lesions at baseline in CROWN study (B7461006)

Intracranial Tumour Response Assessment	**Lorlatinib**	**Crizotinib**
Intracranial overall response in patients with measurable CNS lesions at baseline	**N=17**	**N=13**
Intracranial response rate n (%) (95% CI)[a]	14 (82.4%) (56.6, 96.2)	3 (23.1%) (5.0, 53.8)
Complete response, n (%)	12 (70.6%)	1 (7.7%)
Partial response, n (%)	2 (11.8%)	2 (15.4%)
Duration of intracranial response		
Median, months (95% CI)[b]	NE (NE, NE)	10.2 (9.4, 11.1)
Response duration ≥12 months, n (%)	11 (78.6%)	0
Intracranial overall response in patients with any measurable or non-measurable CNS lesions at baseline	N=38	N=40
Intracranial response rate n (%) (95% CI)[a]	25 (65.8%) (48.6, 80.4)	8 (20.0%) (9.1, 35.6)
Complete response, n (%)	23 (60.5%)	6 (15%)
Partial response, n (%)	2 (5.3%)	2 (5%)
Duration of intracranial response		
Median, months (95% CI)[b]	NE (NE, NE)	9.4 (6.0, 11.1)
Response duration ≥12 months, n (%)	18 (72%)	0

Abbreviations: CI=confidence interval; N/n=number of patients.

[a] Using exact method based on binomial distribution.

[b] Based on the Brookmeyer and Crowley method.

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.

The proportion of patients with improved (≥10-point change from baseline) or stable EORTC QLQ-C30 global QoL was similar between the lorlatinib arm (41.8% and 39.7%, respectively) and crizotinib arm (42.6% and 38.2%, respectively). There were no clinically meaningful (≥10 points) differences between treatment arms in any EORTC QLQ-C30 functioning domain.

Time-to-Deterioration (TTD) in the prespecified composite endpoint of pain in chest, dyspnoea, and cough was not different between treatment arms [HR=1.09, 95% CI: 0.82–1.44;]. In both treatment arms, all 3 lung cancer symptoms improved from baseline with clinically meaningful improvements (≥10-point difference) in cough as early as Cycle 2 and maintained through Cycle 18.

<u>ALK-positive advanced NSCLC previously treated with an ALK kinase inhibitor</u>

The use of lorlatinib in the treatment of ALK-positive advanced NSCLC after treatment with at least one second-generation ALK TKI was investigated in Study A, a single-arm, multicentre Phase 1/2 study and in Study B, a single-arm, multicentre Phase 4 study. In Study A, a total of 139 patients with ALK-positive advanced NSCLC after treatment with at least one second-generation ALK TKI were enrolled in the Phase 2 portion of the study. In Study

B, a total of 71 patients with ALK-positive advanced NSCLC after one prior ALK TKI treatment (alectinib or ceritinib) were enrolled. In bothstudies, patients received lorlatinib orally at the recommended dose of 100 mg once daily, continuously.

In Study A, the primary efficacy endpoint in the Phase 2 portion of the study was ORR, including intracranial (IC)-ORR, as per Independent Central Review (ICR) according to modified response evaluation criteria in solid tumours (modified RECIST v1.1). Secondary endpoints included DOR, IC-DOR, time-to-tumour response (TTR), and PFS. In Study B, the primary efficacy endpoint was ORR, as per ICR according to RECIST v1.1. Secondary endpoints included IC-ORR, DOR, IC-DOR, time-to-tumour response (TTR), time-to-tumour progression (TTP) and PFS.

Patient demographics of the 139 ALK-positive advanced NSCLC patients after treatment with at least one second-generation ALK TKI in Study A were 56% female, 48% White, 38% Asian, and the median age was 53 years (range: 29-83 years) with 16% of patients ≥ 65 years of age. The ECOG performance status at baseline was 0 or 1 in 96% patients. Brain metastases were present at baseline in 67% of patients. Of the 139 patients, 20% received 1 prior ALK TKI, excluding crizotinib, 47% received 2 prior ALK TKIs, and 33% received 3 or more prior ALK TKIs.

Patient demographics of the 71 ALK-positive advanced NSCLC patients who progressed after treatment with one prior ALK TKI (alectinib or ceritinib) with or without chemotherapy in Study B were 42% female, 76% White, 21% Asian, and the median age was 59 years (range: 26-87 years) with 32% of patients ≥ 65 years of age. The ECOG performance status at baseline was 0 in 52% or 1 in 48% of patients. Brain metastases were present at baseline in 42% of patients. Of the 71 patients, 84% received alectinib and 16% received ceritinib as their prior ALK TKIs.

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

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

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

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

[a] Alectinib, brigatinib, or ceritinib.

[b] Pooled efficacy results from Study A and B

[c] Efficacy results from Study A only

[d] Per ICR.

Table 6. Intracranial[*] efficacy results in Study A and Study B by prior treatment

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

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

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

[a] Alectinib, brigatinib, or ceritinib.

[b] Pooled efficacy results from Study A and B

[c] Efficacy results from Study A only

[d] Per ICR.

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

Paediatric population

The Licencing Authority has waived the obligation to submit the results of studies with lorlatinib in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) (see section 4.2 for information on paediatric use).

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 multiple dosing of 100 mg once daily.

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 fasted conditions. Lorlatinib may be administered with or without food.

At 100 mg once daily, the geometric mean (% coefficient of variation [CV]) peak plasma concentration was 577 (42) ng/mL and the AUC_{24} was 5,650 (39) ng·h/mL in patients with cancer. The geometric mean (% CV) oral clearance was 17.7 (39) L/h.

Distribution

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

Biotransformation

In humans, lorlatinib undergoes oxidation and glucuronidation as the primary metabolic pathways. *In vitro* data indicate that lorlatinib is metabolised 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 radiolabelled dose of lorlatinib, a mean 47.7% of the radioactivity was recovered in urine and 40.9% of the radioactivity was recovered in faeces, with overall mean total recovery of 88.6%.

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

Furthermore, lorlatinib is an inducer via human pregnane-X-receptor (PXR) and the human constitutive androstane receptor (CAR).

Linearity/non-linearity

At single dose, lorlatinib systemic exposure (AUC_{inf} and C_{max}) increased in a dose-related manner over the 10 to 200 mg dose range. Few data are available over the 10 to 200 mg dose range; however, no deviation from linearity was observed for AUC_{inf} and C_{max} after single dose.

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.

Also, at steady-state lorlatinib plasma exposures are lower than those expected from single dose pharmacokinetics, indicative of a net time-dependent auto-induction effect.

Hepatic impairment

As lorlatinib is metabolised 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. No information is available for patients with moderate or severe hepatic impairment.

Renal impairment

Less than 1% of the administered dose is detected as unchanged lorlatinib in urine. 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 ($CL_{cr} \geq 30$ mL/min). Based on a renal impairment study, no starting dose adjustments are recommended for patients with mild or moderate renal impairment [eGFR based on Modification of Diet in Renal Disease Study equation (MDRD)-derived eGFR (in mL/min/1.73 m2) × measured body surface area/1.73 ≥ 30 mL/min]. In this study, lorlatinib AUCinf 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 lorlatinib is recommended in patients with severe renal impairment, e.g., a once daily oral starting dose of 75 mg (see section 4.2). No information is available for patients on renal dialysis.

Age, 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, and phenotypes for CYP3A5 and CYP2C19.

Cardiac electrophysiology

In Study A, 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 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 and had a ECG measurement in Study A, lorlatinib was studied in a population of patients that excluded those with QTc interval > 470 msec. In the study population, the maximum mean change from baseline for PR interval was 16.4 msec (2-sided 90% upper CI 19.4 msec) (see sections 4.2, 4.4 and 4.8). Of these, 7 patients had a baseline PR > 200 msec. Among the 284 patients with PR interval < 200 msec, 14% had PR interval prolongation ≥ 200 msec 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).

5.3 Preclinical safety data

Repeat-dose toxicity

The main toxicities observed were inflammation across multiple tissues (skin and cervix of rats and lung, trachea, skin, lymph nodes and/or the oral cavity including mandibular bone of dogs; associated with increases in white blood cells, fibrinogen and/or globulin and decreases in albumin) 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, peripheral nerves and the CNS (potential for cognitive functional impairment) at dose equivalent to human clinical exposure at the recommended posology. Changes in blood pressure and heart rate, and QRS complex and PR interval 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 hepatic bile duct hyperplasia were partially to fully reversible.

Genotoxicity

Lorlatinib is not mutagenic but is aneugenic *in vitro* and *in vivo* with a no observed effect level for aneugenicity approximately 16.5 times human clinical exposure at 100 mg based on AUC.

Carcinogenicity

Carcinogenicity studies have not been conducted with lorlatinib.

Reproductive toxicity

Seminiferous tubular degeneration and/or atrophy in the testes, and epididymal changes (inflammation and/or vacuolation) were observed in the rat and dog. In the prostate, minimal to mild glandular atrophy was observed in dogs at dose equivalent to human clinical exposure at the recommended posology). The effects on male reproductive organs were partially to fully reversible.

In embryo-foetal toxicity studies, conducted in rats and rabbits, respectively, increased embryolethality and lower foetal body weights and malformations were observed. Foetal morphologic abnormalities included rotated limbs, supernumerary digits, gastroschisis, malformed kidneys, domed head, high arched palate and dilation of ventricles of the brain. The exposure at the lowest doses with embryo-foetal effects in animals was equivalent to the human clinical exposure at 100 mg, based on AUC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Calcium hydrogen phosphate
Sodium starch glycolate
Magnesium stearate

Film-coating

Hypromellose
Lactose monohydrate

Macrogol
Triacetin
Titanium dioxide (E171)
Iron oxide black (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
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6.5 Nature and contents of container

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

Each pack contains 90 film-coated tablets in 9 blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00057/1674

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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