ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lorviqua 25 mg film-coated tablets
Lorviqua 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lorviqua 25 mg film-coated tablets

Each film-coated tablet contains 25 mg of lorlatinib.

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

Lorviqua 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of lorlatinib.

Excipient with known effect
Each film-coated tablet contains 4.20 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Lorviqua 25 mg film-coated tablets

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

Lorviqua 100 mg film-coated tablets

Oval (8.5 × 17 mm) dark pink immediate release film-coated tablet, debossed with "Pfizer" on one side and "LLN 100" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
- crizotinib and at least one other ALK TKI.

4.2 Posology and method of administration

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

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 effects (changes in cognition, mood 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 OR Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.

Table 1. Recommended lorlatinib dose modifications for adverse reactions

Adverse reaction[a]	Lorlatinib dosing
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
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: CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; HMG CoA=3-hydroxy-3-methylglutaryl coenzyme A; NCI=National Cancer Institute; 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 (CL_{cr}: ≥ 30mL/min) renal impairment based on a population pharmacokinetic analysis. Information for lorlatinib use in patients with severe (CL_{cr}: < 30 mL/min) renal impairment is very limited. Therefore, lorlatinib is not recommended in patients with severe renal impairment (see section 5.2).

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). Median time of occurrence of severe increase in serum cholesterol and triglycerides is 201 days (range: 42 to 518 days) and 127 days (range: 15 to 358 days), respectively. 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

Central nervous system (CNS) effects have been observed in patients receiving lorlatinib, including changes in cognitive function, mood or speech (see section 4.8). Dose modification or discontinuation may be required for those patients who develop CNS effects (see section 4.2).

Atrioventricular block

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

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

Lipase and amylase increase

Elevations of lipase and/or amylase have occurred in patients receiving lorlatinib (see section 4.8). Median time of occurrence of increase in serum lipase and amylase is 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).

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).

Drug-drug interactions

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 (see sections 4.3 and 4.5).

Concomitant use with moderate CYP3A4/5 inducers should be avoided, if possible, as they may also reduce lorlatinib plasma concentrations (see section 4.5).

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

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.

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) 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). Concomitant use with moderate CYP3A4/5 inducers should be avoided, if possible, as they may also reduce lorlatinib plasma concentrations (see section 4.4).

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 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).

Medicinal products whose plasma concentrations may be altered by lorlatinib

CYP3A4/5 substrates
In vitro studies indicated that lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A4/5 and it activates the human pregnane-X-receptor (PXR), with the net effect *in vivo* being induction. Concurrent administration of lorlatinib in patients resulted in decreased oral midazolam AUC when midazolam was administered alone, suggesting that lorlatinib is 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).

In vitro studies of other CYP inhibition and induction
Lorlatinib may have the potential to inhibit CYP2C9.

In vitro studies also indicated that lorlatinib is an inducer of CYP2B6 and activates the human constitutive androstane receptor (CAR). Concomitant administration of lorlatinib with CYP2B6 substrates (e.g. bupropion, efavirenz) may result in reduced plasma concentrations of the CYP2B6 substrate. *In vitro*, lorlatinib has a low potential to cause drug-drug interactions by induction of CYP1A2.

In vitro studies of UGT inhibition
In vitro studies indicated that lorlatinib may have the potential to inhibit UGT1A1.

In vitro studies with drug transporters
In vitro studies indicated that lorlatinib may have the potential to inhibit P-glycoprotein (P-gp, systemically and at the gastrointestinal [GI] tract), BCRP (GI tract), OATP1B1, OATP1B3, OCT1, MATE1 and OAT3 at clinically relevant concentrations.

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 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%) and mood effects (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 reaction that led to permanent discontinuations was cognitive effects.

Tabulated list of adverse reactions

Table 2 presents adverse reactions occurring in 295 adult patients treated with lorlatinib 100 mg once daily with advanced NSCLC from Study A.

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	15.9	5.1
Metabolism and nutrition disorders			
Hypercholesterolaemia[a]	Very common	84.4	16.6
Hypertriglyceridaemia[b]	Very common	67.1	16.6
Psychiatric disorders			
Mood effects[c]	Very common	22.7	1.7
Hallucinations[d]	Common	7.8	1.0
Nervous system disorders			
Cognitive effects[e]	Very common	28.8	2.0
Peripheral neuropathy[f]	Very common	47.8	2.7
Headache	Very common	18.0	0.7
Speech effects[g]	Common	9.8	0.3
Eye disorders			
Vision disorder[h]	Very common	15.3	0.3
Respiratory, thoracic and mediastinal disorders			
Pneumonitis[i]	Common	1.4	1.0
Gastrointestinal disorders			
Diarrhoea	Very common	22.7	1.0
Nausea	Very common	18.3	0.7
Constipation	Very common	15.9	0
Skin and subcutaneous tissue disorders			
Rash[j]	Very common	14.2	0.3
Musculoskeletal and connective tissue disorders			
Arthralgia	Very common	24.7	0.7
Myalgia[k]	Very common	19.3	0
General disorders and administration site conditions			
Oedema[l]	Very common	54.6	2.4
Fatigue[m]	Very common	28.1	0.7
Investigations			
Weight increased	Very common	26.4	5.4
Lipase increased	Very common	13.9	8.8
Amylase increased	Very common	10.2	3.1
Electrocardiogram PR prolongation	Uncommon	0.7	0

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

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

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

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

[d] Hallucinations (including auditory hallucination, hallucination, visual hallucination).

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

[f] Peripheral neuropathy (including burning sensation, carpal tunnel syndrome, dysaesthesia, formication, gait disturbance, hypoaesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity,

paraesthesia, 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, 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 84.4% and 67.1% of patients, respectively. Of those, mild or moderate adverse reactions of hypercholesterolaemia or hypertriglyceridaemia occurred in 67.8% and 50.5% of patients, respectively (see section 4.4). The median time to onset for both hypercholesterolaemia and hypertriglyceridaemia was 15 days (range: 1 to 399 days). The median duration of hypercholesterolaemia and hypertriglyceridaemia was 381 and 405 days, respectively.

Central nervous system effects
CNS adverse reactions were primarily cognitive effects (28.8%), mood effects (22.7%), and speech effects (9.8%), and were generally mild, transient, and reversible spontaneously 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 effect 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%). Median time to onset for cognitive, mood and speech effects was 92, 44 and 42 days, respectively. Median duration of cognitive, mood and speech effects was 224, 83 and 106 days, respectively.

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 national reporting system listed in Appendix V.

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: L01XE44

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
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. 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. Patients received lorlatinib 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 (IC)-ORR, as per Independent Central Review (ICR) according to modified response evaluation criteria in solid tumours (modified RECIST version 1.1). Secondary endpoints included duration of response (DOR), IC-DOR, time-to-tumour response (TTR), and progression-free survival (PFS).

Patient demographics of the 139 ALK-positive advanced NSCLC patients after treatment with at least one second-generation ALK TKI, 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 Eastern Cooperative Oncology Group (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.

The main efficacy results for Study A are included in Tables 3 and 4.

Table 3. Overall efficacy results in Study A by prior treatment

Efficacy parameter	**One prior ALK TKI[a] with or without prior chemotherapy (N = 28)**	**Two or more prior ALK TKIs with or without prior chemotherapy (N = 111)**
Objective response rate[b]	42.9%	39.6%
(95% CI)	(24.5, 62.8)	(30.5, 49.4)
Complete response, n	1	2
Partial response, n	11	42
Duration of response		
Median, months	5.6	9.9
(95% CI)	(4.2, NR)	(5.7, 24.4)
Progression-free survival		
Median, months	5.5	6.9
(95% CI)	(2.9, 8.2)	(5.4, 9.5)

Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; ICR=Independent Central Review; N/n=number of patients; NR=not reached; TKI=tyrosine kinase inhibitor.
[a] Alectinib, brigatinib, or ceritinib.
[b] Per ICR.

Table 4. Intracranial* efficacy results in Study A by prior treatment

Efficacy parameter	One prior ALK TKI[a] with or without prior chemotherapy (N = 9)	Two or more prior ALK TKIs with or without prior chemotherapy (N = 48)
Objective response rate[b]	66.7%	52.1%
(95% CI)	(29.9, 92.5)	(37.2, 66.7)
Complete response, n	2	10
Partial response, n	4	15
Duration of intra-cranial response		
Median, months	NR	12.4
(95% CI)	(4.1, NR)	(6.0, NR)

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

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

[a] Alectinib, brigatinib, or ceritinib.

[b] Per ICR.

In the overall efficacy population of 139 patients, 56 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 49.1% (95% CI: 35.1, 63.2) and 31.5% for non-Asians (95% CI: 21.1, 43.4). Among the 31 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 54.5% for Asians (95% CI: 32.2, 75.6) and 46.4% for non-Asians (95% CI: 27.5, 66.1).

Paediatric population

The European Medicines Agency 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).

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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.

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.

At steady-state, the systemic exposure (AUC_{24} and C_{max}) increased less than proportionally over the 10 to 200 mg dose range.

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} > 30 mL/min). No starting dose adjustments are recommended for patients with mild or moderate renal impairment. Information for lorlatinib use in patients with severe renal impairment (CL_{cr} < 30 mL/min) is limited (n = 1).

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.

6.5 Nature and contents of container

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

Lorviqua 25 mg film-coated tablets

Each pack contains 90 film-coated tablets in 9 blisters or 120 film-coated tablets in 12 blisters.

Lorviqua 100 mg film-coated tablets

Each pack contains 30 film-coated tablets in 3 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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1355/001
EU/1/19/1355/002
EU/1/19/1355/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 May 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of lorlatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study CROWN (1006) comparing lorlatinib versus crizotinib for the first-line treatment of advanced ALK-positive NSCLC. The clinical study report will be submitted by:	31 December 2021
In order to further confirm the efficacy of lorlatinib in patients who progressed after alectinib or ceritinib as the first ALK TKI therapy, the MAH should conduct a prospective single arm study investigating patients in that same setting. The clinical study report will be submitted by:	30 June 2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lorviqua 25 mg film-coated tablets
lorlatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg of lorlatinib.

3. LIST OF EXCIPIENTS

Contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

90 film-coated tablets
120 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1355/001 (120 film-coated tablets)
EU/1/19/1355/003 (90 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lorviqua 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lorviqua 25 mg tablets
lorlatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lorviqua 100 mg film-coated tablets
lorlatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of lorlatinib.

3. LIST OF EXCIPIENTS

Contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1355/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lorviqua 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lorviqua 100 mg tablets
lorlatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Lorviqua 25 mg film-coated tablets
Lorviqua 100 mg film-coated tablets
lorlatinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

What is in this leaflet

1. What Lorviqua is and what it is used for
2. What you need to know before you take Lorviqua
3. How to take Lorviqua
4. Possible side effects
5. How to store Lorviqua
6. Contents of the pack and other information

1. What Lorviqua is and what it is used for

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

What Lorviqua is used for
Lorviqua can be prescribed to you if
- you have been previously treated with a medicine called alectinib or ceritinib, which are ALK inhibitors; or
- you have been previously treated with crizotinib followed by another ALK inhibitor.

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

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

2. What you need to know before you take Lorviqua

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

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

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

Tell your doctor immediately if you develop:
- heart problems. Tell your doctor right away about changes in your heart beat (fast or slow), light-headedness, fainting, dizziness or shortness of breath. These symptoms could be signs of heart problems. Your doctor may check for problems with your heart during treatment with Lorviqua. If the results are abnormal, your doctor may decide to reduce the dose of Lorviqua or stop your treatment.
- speech problems, difficulty speaking, including slurred or slow speech. Your doctor may investigate further and may decide to reduce your dose of Lorviqua or stop your treatment.
- mood or memory problems, such as change in your mood (including depression, euphoria and mood swings), irritability, aggression, agitation, anxiety or a change in your personality and episodes of confusion. Your doctor may investigate further and may decide to reduce your dose of Lorviqua or stop your treatment.
- pain in the back or abdomen (belly), yellowing of the skin and eyes (jaundice), nausea or vomiting. These symptoms could be signs of pancreatitis. Your doctor may investigate further and may decide to reduce the dose of Lorviqua.
- cough, chest pain, or a worsening of existing respiratory symptoms. Your doctor may investigate further and treat you with other medicines such as antibiotics and steroids. Your doctor may decide to reduce your dose of Lorviqua or stop your treatment.

Your doctor may do further assessments and may decide to reduce the dose of Lorviqua or stop your treatment if you develop:
- liver problems. Tell your doctor right away if you feel more tired than usual, your skin and whites of your eyes turn yellow, your urine turns dark or brown (tea colour), you have nausea, vomiting, or decreased appetite, you have pain on the right side of your stomach, you have itching, or if you bruise more easily than usual. Your doctor may do blood tests to check your liver function.

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

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

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

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

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

In particular tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- boceprevir – a medicine used to treat hepatitis C.
- buproprion – a medicine used to treat depression or to help people quit smoking.
- dihydroergotamine, ergotamine – medicines used to treat migraine headaches.
- efavirenz, cobicistat, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either elvitegravir, indinavir, lopinavir or tipranavir – medicines used to treat AIDS/HIV.
- ketoconazole, itraconazole, voriconazole, posaconazole – medicines used to treat fungal infections. Also troleandomycin, a medicine used to treat certain types of bacterial infections.
- quinidine – a medicine used to treat irregular heartbeat and other heart problems.
- pimozide – a medicine used to treat mental health problems.
- alfentanil and fentanyl – medicines used to treat severe pain.
- ciclosporin, sirolimus, and tacrolimus – medicines used in organ transplantation to prevent organ rejection.

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

Pregnancy, breast-feeding and fertility

- **Contraception – information for women**
  You should not become pregnant while taking this medicine. If you are able to have children, you must use highly effective contraception (for example, double-barrier contraception such as condom and diaphragm) while on treatment and for at least 5 weeks after stopping treatment. Lorlatinib may reduce the effectiveness of hormonal contraceptive methods (for example, birth control pill); therefore, hormonal contraceptives may not be considered highly effective. If hormonal contraception is unavoidable it must be used in combination with a condom. Talk to your doctor about the right methods of contraception for you and your partner.
- **Contraception – information for men**
  You should not father children during treatment with Lorviqua because this medicine could harm the baby. If there is any possibility that you may father a child while taking this medicine, you must use a condom during treatment, and for at least 14 weeks after completing therapy. Talk to your doctor about the right methods of contraception for you and your partner.
- **Pregnancy**
  - Do not take Lorviqua if you are pregnant. This is because it may harm your baby.
  - If your male partner is being treated with Lorviqua, he must use a condom during treatment and for at least 14 weeks after completing therapy.
  - If you become pregnant when taking the medicine or during the 5 weeks after taking your last dose, tell your doctor straight away.

- **Breast-feeding**
  Do not breast-feed while taking this medicine and for 7 days after the last dose. This is because it is not known if Lorviqua can pass into breast milk and could therefore harm your baby.
- **Fertility**
  Lorviqua may affect male fertility. Talk to your doctor about fertility preservation before taking Lorviqua.

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

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

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

3. How to take Lorviqua

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

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

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

If you forget to take Lorviqua
What to do if you forget to take a tablet depends on how long it is until your next dose.
- If your next dose is in 4 hours or more, take the missed tablet as soon as you remember. Then take the next tablet at the usual time.
- If your next dose is in less than 4 hours away, skip the missed tablet. Then take the next tablet at the usual time.

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

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

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

4. Possible side effects

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

Some side effects could be serious.

Tell your doctor straight away if you notice any of the following side effects (also section 2 **What you need to know before you take Lorviqua**). Your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely:
- cough, shortness of breath, chest pain, or worsening breathing problems
- slow pulse, (50 beats per minute or less), feeling tired, dizzy or faint, or losing consciousness
- abdominal (belly) pain, back pain, nausea, vomiting, itching, yellowing of the skin and eyes
- mental status changes; changes in cognition including confusion, memory loss, and reduced ability to concentrate; changes in mood including irritability and mood swings; and changes in speech including difficulty speaking, such as slurred or slow speech

Other side effects of Lorviqua may include:

Very common: may affect more than 1 in 10 people
- increase in cholesterol and triglycerides (fats in your blood that would be detected during blood tests)
- limb or skin swelling
- problems with your eyes, such as difficulty seeing out of one or both eyes, double vision, or perceived flashes of light
- problems with the nerves in your arms and legs, such as pain, numbness, unusual sensations like burning or pins and needles, difficulty walking, or difficulty with usual activities of daily living such as writing
- increased level of enzymes called lipase and/or amylase in the blood that would be detected during blood tests
- low number of red blood cells known as anaemia that would be detected during blood tests
- diarrhoea
- constipation
- pain in your joints
- weight gain
- headache
- rash
- muscle pain

Common: may affect up to 1 in 10 people
- hallucinations (seeing or hearing things that are not there)

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

5. How to store Lorviqua

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

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

This medicine does not require any special storage conditions.

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

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

6. Contents of the pack and other information

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

- The other ingredients are:
  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), and iron oxide red (E172).

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

What Lorviqua looks like and contents of the pack
Lorviqua 25 mg is supplied as round light pink film-coated tablets, debossed with "Pfizer" on one side and "25" and "LLN" on the other side.
Lorviqua 25 mg is provided in blisters of 10 tablets, which are available in packs containing 90 tablets (9 blisters) or 120 tablets (12 blisters).

Lorviqua 100 mg is supplied as oval dark pink film-coated tablets, debossed with "Pfizer" on one side and "LLN 100" on the other side.
Lorviqua 100 mg is provided in blisters of 10 tablets, which are available in packs containing 30 tablets (3 blisters).

Not all pack sizes may be marketed.

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This leaflet was last revised in {**MM/YYYY**}.

This medicine has been given 'conditional approval'.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.