▼ This medicinal product is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - LORVIQUA® (LORLATINIB)

1. NAME OF THE MEDICINE

Lorlatinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25 mg film-coated tablet contains 25 mg of lorlatinib.
Excipient with known effect: 1.58 mg of lactose per film-coated tablet.

Each 100 mg film-coated tablet contains 100 mg of lorlatinib.
Excipient with known effect: 4.20 mg of lactose per film-coated tablet.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Tablet, film coated.

25 mg: 8 mm round tan film-coated tablet, debossed with “Pfizer” on one side and “25” and “LLN” on the other side.

100 mg: oval (8.5 × 17 mm) lavender film-coated tablet, debossed with “Pfizer” on one side and “LLN 100” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LORVIQUA has **provisional approval** in Australia for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed on

- crizotinib and at least one other ALK inhibitor; or
- alectinib as the first ALK inhibitor therapy; or
- ceritinib as the first ALK inhibitor therapy.

The decision to approve this indication has been made on the basis of tumour response rate and duration of response in a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial.

4.2 Dose and method of administration

ALK-positive status should be established using a validated ALK assay prior to initiation of lorlatinib therapy.

Recommended dosing

The recommended dose of LORVIQUA is 100 mg taken orally once daily. Continue treatment for as long as the patient is deriving clinical benefit from therapy.

LORVIQUA may be taken with or without food (see Section 5.2).

Patients should be encouraged to take their dose of LORVIQUA at approximately the same time each day. Tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked or otherwise not intact.

If a dose of 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 and/or dose reduction may be required based on individual safety and tolerability. Dose reduction levels are summarised below.

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

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

Dose modification recommendations for toxicities and for patients who develop first-degree, second-degree, or complete atrioventricular (AV) block are provided in Table 1.

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Reactions

Adverse Reaction	LORVIQUA Dosing
Hypercholesterolaemia or Hypertriglyceridaemia	
Mild hypercholesterolaemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L) OR Moderate hypercholesterolaemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L)	Introduce or modify lipid-lowering therapy[a] in accordance with respective prescribing information; continue LORVIQUA at same dose.

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Reactions

Adverse Reaction	**LORVIQUA Dosing**
Mild hypertriglyceridaemia (triglycerides between 150 and 300 mg/dL or 1.71 and 3.42 mmol/L) OR Moderate hypertriglyceridaemia (triglycerides between 301 and 500 mg/dL or 3.43 and 5.7 mmol/L)	
Severe hypercholesterolaemia (cholesterol between 401 and 500 mg/dL or between 10.35 and 12.92 mmol/L) OR Severe hypertriglyceridaemia (triglycerides between 501 and 1,000 mg/dL or 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[a]; if currently on lipid-lowering therapy, increase the dose of this therapy[a] in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue LORVIQUA at the same dose without interruption.
Life-threatening hypercholesterolaemia (cholesterol over 500 mg/dL or over 12.92 mmol/L) OR Life-threatening hypertriglyceridaemia (triglycerides over 1,000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[a] or increase the dose of this therapy[a] in accordance with respective prescribing information or change to a new lipid-lowering therapy. Withhold LORVIQUA until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to moderate or mild severity grade. Re-challenge at same LORVIQUA dose while maximising lipid-lowering therapy[a] in accordance with respective prescribing information. If severe hypercholesterolaemia and/or hypertriglyceridaemia recur despite maximal lipid-lowering therapy[a] in accordance with respective prescribing information, reduce LORVIQUA by 1 dose level.
Central Nervous System Effects[b,c]	
Grade 2: Moderate OR Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume LORVIQUA at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue LORVIQUA.
Lipase/Amylase Increase	
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Withhold LORVIQUA until lipase or amylase returns to baseline. Then resume LORVIQUA at 1 reduced dose level.

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Reactions

Adverse Reaction	**LORVIQUA Dosing**
Interstitial Lung Disease (ILD)/Pneumonitis	
Grade 1: Mild OR Grade 2: Moderate	Withhold LORVIQUA until symptoms have returned to baseline and consider initiating corticosteroids. Resume LORVIQUA at 1 reduced dose level. Permanently discontinue LORVIQUA if ILD/pneumonitis recurs or fails to recover after 6 weeks of LORVIQUA hold and steroid treatment.
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue LORVIQUA.
PR interval prolongation/Atrioventricular (AV) block	
First-degree AV block: Asymptomatic	Continue LORVIQUA at the same dose without interruption. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to heart block closely.
First-degree AV block: Symptomatic	Withhold LORVIQUA. 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 LORVIQUA at 1 reduced dose level.
Second-degree AV block: Asymptomatic	Withhold LORVIQUA. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to heart block closely. If subsequent ECG does not show second-degree AV block, resume LORVIQUA at 1 reduced dose level.
Second-degree AV block: Symptomatic	Withhold LORVIQUA. 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 LORVIQUA at 1 reduced dose level.
Complete AV block	Withhold LORVIQUA. 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

Table 1. Recommended LORVIQUA Dose Modifications for Adverse Reactions

Adverse Reaction	LORVIQUA Dosing
	be considered. If pacemaker placed, resume LORVIQUA at full dose. If no pacemaker placed, resume LORVIQUA at 1 reduced dose level only when symptoms resolve and PR interval is less than 200 msec.
Other adverse reactions[c]	
Grade 1 OR Grade 2	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3	Withhold LORVIQUA until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume LORVIQUA at 1 reduced dose level.

Abbreviations: CNS=central nervous system; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; HMG CoA=3-hydroxy-3-methylglutaryl coenzyme A; ULN=upper limit of normal.

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

[b] Examples of CNS effects comprise hallucination and changes in cognition, mood, mental status, or speech (see sections 4.4 and 4.8).

[c] Grade categories are based on CTCAE classifications.

Strong cytochrome P-450 (CYP) 3A inhibitors

Concurrent use of LORVIQUA with strong CYP3A inhibitors may increase lorlatinib plasma concentrations. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered (see Sections 4.5 and 5.2). If a strong CYP3A inhibitor must be co-administered, the starting LORVIQUA dose of 100 mg once daily should be reduced to once daily 75 mg dose. If concurrent use of a strong CYP3A inhibitor is discontinued, LORVIQUA should be resumed at the dose used prior to the initiation of the strong CYP3A inhibitor and after a washout period of 3 to 5 half-lives of the strong CYP3A inhibitor.

Hepatic impairment

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

Renal impairment

No dose adjustment is needed for patients with mild or moderate (creatinine clearance [CL_{cr}]:

Therefore, LORVIQUA is not recommended in patients with severe renal impairment (see Section 5.2).

Elderly (³ 65 years)

The limited data on the safety and efficacy of LORVIQUA in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see Section 5.2).

Paediatric patients

The safety and efficacy of LORVIQUA in paediatric patients has not been established.

4.3 Contraindications

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

Concomitant use of strong CYP3A inducers with LORVIQUA is contraindicated due to the potential for serious hepatotoxicity (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] elevations) (see Sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

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

Hyperlipidaemia

The use of LORVIQUA has been associated with increases in serum cholesterol and triglycerides (see Section 4.8). Serum cholesterol and triglycerides should be monitored before initiation with LORVIQUA, for 2, 4, and 8 weeks after initiating LORVIQUA and periodically thereafter. Initiation, or increase in the dose, of lipid-lowering agents is required (see Section 4.2).

Central nervous system effects

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

Atrioventricular block

PR interval prolongation and AV block events have been reported in patients receiving LORVIQUA. Monitor electrocardiogram (ECG) prior to initiating LORVIQUA and monthly thereafter, particularly in patients with predisposing conditions to the occurrence of clinically significant cardiac events. Dose modification may be required for those patients who develop AV block (see Section 4.2).

Lipase and amylase increase

Elevations of lipase and/or amylase have occurred in patients receiving lorlatinib (see section 4.8). Median time of occurrence of increase in serum lipase and amylase is 70 days (range: 7 to

696 days) and 41 days (range: 7 to 489 days), respectively. Risk of pancreatitis should be considered in patients receiving lorlatinib due to concomitant hypertriglyceridaemia 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 (ILD)/Pneumonitis

Severe or life-threatening pulmonary adverse reactions consistent with pneumonitis have occurred with lorlatinib (see Section 4.8). Any patient who presents with worsening of respiratory symptoms indicative of pneumonitis (e.g. dyspnoea, cough, and fever) should be promptly evaluated for pneumonitis. LORVIQUA should be withheld and/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 LORVIQUA and rifampicin, a strong CYP3A inducer, was associated with increases of ALT and AST with no increase of total bilirubin and alkaline phosphatase (see Section 4.5). Concomitant use of a strong CYP3A inducer is contraindicated (see Sections 4.3 and 4.5). Any strong CYP3A inducers have to be discontinued for at least 3 plasma half-lives of the strong CYP3A inducer before LORVIQUA treatment is started.

Avoid concomitant use of LORVIQUA with moderate CYP3A inducers. If concomitant use of moderate CYP3A inducers cannot be avoided, monitor AST, ALT, and bilirubin 48 hours after initiating LORVIQUA and at least 3 times during the first week after initiating LORVIQUA.

Depending upon the relative importance of each drug, discontinue LORVIQUA or the CYP3A inducer for persistent Grade 2 or higher hepatotoxicity.

Fertility and pregnancy

Based on animal data and mechanism of action, there is a risk of fetal harm if exposed to LORVIQUA (see Sections 5.1 and 5.3). Women of childbearing potential should be advised to avoid becoming pregnant while receiving LORVIQUA. A highly effective non-hormonal method of contraception is required for female patients during treatment with LORVIQUA because lorlatinib can render hormonal contraceptives ineffective (see Sections 4.5 and 4.6). If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 21 days after completing therapy.

During treatment with LORVIQUA and for at least 14 weeks after the final dose, male patients with female partners of reproductive potential must use effective contraception, including a condom, and male patients with pregnant partners must use condoms (see Section 4.6). Male fertility may be compromised during treatment with LORVIQUA (see Section 5.3). Men should seek advice on effective fertility preservation before treatment.

4.5 Interactions with other medicines and other forms of interaction

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

CYP3A inhibitors

Itraconazole, a strong inhibitor of CYP3A, administered at a dose of 200 mg once daily for 5 days, increased the mean area under the curve (AUC) 42% and C_{max} 24% of a single 100 mg oral dose of lorlatinib in healthy volunteers. Concomitant administration of LORVIQUA with strong CYP3A inhibitors (e.g., boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, telaprevir, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either danoprevir, elvitegravir, indinavir, lopinavir, saquinavir, or tipranavir) may increase lorlatinib plasma concentrations. Grapefruit products may also increase lorlatinib plasma concentrations. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered. If a strong CYP3A inhibitor must be concomitantly administered, a dose reduction of LORVIQUA is recommended (see Section 4.2).

CYP3A inducers

Rifampicin, a strong inducer of CYP3A, administered at a dose of 600 mg once daily for 9 days, reduced the mean lorlatinib AUC by 85% and C_{max} by 76% of a single 100 mg dose of lorlatinib in healthy volunteers; increases in liver function tests (AST and ALT) were also observed. Concomitant administration of LORVIQUA with strong CYP3A inducers (e.g., rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's wort) may decrease lorlatinib plasma concentrations. The use of a strong CYP3A inducer with LORVIQUA is contraindicated (see Section 4.3 and 4.4). Any strong CYP3A inducers have to be discontinued for at least 3 plasma half-lives of the strong CYP3A inducer before treatment with LORVIQUA is started. Concomitant use with moderate CYP3A inducers should be avoided, if possible, as they may also reduce lorlatinib plasma concentrations.

Proton-Pump inhibitors, H_2-receptor antagonists, or locally acting antacids

The proton-pump inhibitor rabeprazole had a minimal effect on lorlatinib plasma exposure (90% confidence interval [CI] for the AUC_{inf} ratio, expressed as a percentage: 97.6%, 104.3%). No dose adjustment is required when LORVIQUA is taken with proton-pump inhibitors, H_2-receptor antagonists, or locally acting antacids.

Drugs whose plasma concentrations may be altered by lorlatinib

CYP3A substrates

Lorlatinib has a net induction effect on CYP3A both *in vitro* and *in vivo*. . Lorlatinib 150 mg orally once daily for 15 days decreased AUC_{inf} by 64% and C_{max} by 50% of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate).Thus, concurrent administration of LORVIQUA with CYP3A substrates with narrow therapeutic indices, including but not limited to hormonal contraceptives, alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl,

pimozide, quinidine, sirolimus, and tacrolimus, should be avoided since the concentration of these drugs may be reduced by lorlatinib.

In vitro studies of other CYP inhibition and induction

In vitro studies indicated that clinical drug-drug interactions as a result of lorlatinib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 are unlikely to occur.

In vitro studies also indicated that lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A and it activates the human pregnane-X-receptor (PXR), with the net effect *in vivo* being induction. *In vitro* studies also indicated that lorlatinib is an inducer of CYP2B6 and activates the human constitutive androstane receptor (CAR). Concomitant administration of LORVIQUA with CYP2B6 substrates (e.g. bupropion, efavirenz) may result in reduced plasma concentrations of the CYP2B6 substrate. Lorlatinib might also induce CYP2C and reduce plasma concentrations of CYP2C substrates. *In vitro*, lorlatinib has a low potential to cause drug-drug interactions by induction of CYP1A2.

In vitro, the major circulating metabolite (M8) of lorlatinib showed a low potential to cause drug-drug interaction by inhibiting CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, or by inducing CYP1A2, CYP2B6, and CYP3A.

In vitro studies of UDP-glucuronylsyltransferase (UGT) inhibition

In vitro studies indicated that clinical drug-drug interactions as a result of lorlatinib-mediated inhibition of the metabolism of substrates for UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15 are unlikely to occur.

In vitro studies indicated that clinical drug-drug interactions as a result of M8-mediated inhibition of the metabolism of substrates for UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 are unlikely to occur.

In vitro studies with drug transporters

In vitro studies indicated that clinical drug-drug interactions as a result of lorlatinib-mediated inhibition of breast cancer resistance protein (BCRP, systemically), multidrug and toxin extrusion protein (MATE)2K, organic anion transporter (OAT)1, organic cation transporter (OCT)2 and organic anion transporting polypeptide OATP1B1 and OATP1B3 are unlikely. Lorlatinib may have the potential to inhibit P-glycoprotein (P-gp, systemically and at the gastrointestinal [GI] tract), BCRP (GI tract), OCT1, MATE1, and OAT3 at clinically relevant concentrations.

In vitro studies indicated that clinical drug-drug interactions as a result of M8-mediated inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K are unlikely to occur.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females and males

Women of childbearing potential should be advised to avoid becoming pregnant while receiving LORVIQUA. A highly effective non-hormonal method of contraception is required for female patients during treatment with LORVIQUA, because lorlatinib can render hormonal contraceptives ineffective (see Sections 4.4 and 4.5). If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 21 days after completing therapy.

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

Effects on fertility

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

Based on nonclinical safety findings, male fertility may be compromised during treatment with LORVIQUA. It is not known whether LORVIQUA affects female fertility. Men should seek advice on effective fertility preservation before treatment.

Use in pregnancy – Pregnancy Category D

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

Administration of lorlatinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in embryolethality, abortions and malformations. Fetal morphologic abnormalities included rotated limbs, supernumerary digits, gastroschisis, malformed kidneys, domed head, high arched palate, and dilation of ventricles of the brain. The lowest doses with embryo-fetal effects in animals correlated with 0.6 to 1.1 times the human clinical exposure at 100 mg, based on AUC.

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

Use in lactation

It is not known whether lorlatinib and its metabolites are excreted in human milk. A risk to the newborn child cannot be excluded.

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

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 Adverse effects (undesirable effects)

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

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

The most frequently reported adverse reactions were hypercholesterolaemia (84.4%), hypertriglyceridaemia (67.1%), oedema (54.6%), peripheral neuropathy (47.8%), cognitive effects (28.8%), fatigue (28.1%), weight increased (26.4%), 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 a permanent discontinuation was hallucinations.

Serious adverse reactions were reported in 7.8% patients receiving lorlatinib. The most frequent serious adverse reaction reported was cognitive effects (1.0%).

Table 2 presents adverse drug reactions for LORVIQUA by system organ class (SOC) and CIOMS frequency categories, defined using the following convention: very common (³ 1/10), common (³ 1/100 to < 1/10), uncommon (³ 1/1,000 to < 1/100), rare (³ 1/10,000 to < 1/1,000), very rare (<1/10,000). Within each SOC and frequency category, undesirable effects are presented in order of decreasing medical seriousness or clinical importance.

Table 2. Adverse Drug Reactions

System Organ Class and Adverse Drug 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

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in the table above. Terms actually reported in the studies up to the data cutoff date (02Feb2018) 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 hallucination, hallucination auditory, hallucination visual).
[e] Cognitive effects (including events from SOC Nervous system disorders: amnesia, cognitive disorder, dementia, disturbance in attention, memory impairment, mental impairment; and also including events from SOC Psychiatric disorders: attention deficit/hyperactivity disorder, confusional state, delirium, disorientation, reading disorder). Within these effects, terms from SOC Nervous system disorders were more frequently reported than terms from SOC Psychiatric disorders.
[f] Peripheral neuropathy (including burning sensation, 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 (including dysarthria, slow speech, speech disorder).
[h] Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).
[i] Pneumonitis (including interstitial lung disease, pneumonitis).
[j] Rash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash).
[k] Myalgia (including muscular skeletal 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

In Study B7461001, adverse reactions of increase in serum cholesterol or triglycerides were reported in 84.4% and 67.1% of patients, respectively. Mild or moderate adverse reactions of hypercholesterolaemia or hypertriglyceridaemia occurred in 67.8% and 50.5% of patients, respectively. No patient was discontinued from treatment with lorlatinib due to hypercholesterolaemia or hypertriglyceridaemia (see Sections 4.2 and 4.4). The median time to onset for both hypercholesterolaemia and hypertriglyceridaemia was 15 days. The median duration of hypercholesterolaemia and hypertriglyceridaemia was 381 and 405 days, respectively.

Nervous system disorders

In Study B7461001, 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 upon dose delay and/or dose reduction (see Sections 4.2 and 4.4). The most common cognitive effect of any grade was memory impairment (11.5%), and the most common Grade 3 or 4 reactions were cognitive disorder and confusional state (0.7% each). The most common mood effect of any grade was irritability (6.1%), which was also the most common Grade 3 or 4 reaction (1.0%). The most common speech effect of any grade was dysarthria (4.1%), and the most common Grade 3 or 4 reaction was slow speech (0.3%). 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 registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Lorlatinib is an adenosine triphosphate (ATP)-competitive, brain-penetrant, small molecule inhibitor of ALK and ROS1 tyrosine kinases that addresses mechanisms of resistance following previous treatment with ALK inhibitor therapy.

In nonclinical studies, lorlatinib inhibited catalytic activities of non-mutated ALK and a broad range of clinically relevant ALK mutant kinases in recombinant enzyme and cell-based assays. The ALK mutations analyzed included those conferring resistance to other ALK inhibitors, including alectinib, brigatinib, ceritinib, and crizotinib.

Lorlatinib demonstrated anti-tumour activity at nanomolar free plasma concentrations in mice bearing tumor xenografts that express echinoderm microtubule-associated protein-like 4 (EML4) fusions with ALK variant 1 (v1), including ALK mutations L1196M, G1269A, G1202R, and I1171T. Two of these ALK mutants, G1202R and I1171T, are known to confer resistance to first and second generation ALK inhibitors. Lorlatinib is also capable of penetrating the blood-brain barrier and achieved efficacious brain exposure in mice and rat. In mice bearing orthotopic EML4-ALK or EML4-ALK^{L1196M} brain tumour implants, lorlatinib caused tumour shrinkage and prolonged survival. The overall anti-tumour efficacy of lorlatinib was dose-dependent and strongly correlated with inhibition of ALK phosphorylation.

Clinical studies

The use of LORVIQUA in the treatment of ALK-positive advanced NSCLC previously treated with 1 or more ALK TKIs was investigated in Study B7461001, a single-arm, multicenter Phase 1/2 study. A total of 197 patients with ALK-positive advanced NSCLC previously treated with 1 or more ALK TKIs were enrolled in the Phase 2 portion of the study. Eligible patients had evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC that carried an ALK rearrangement, as determined by fluorescence in situ hybridization (FISH) assay or by Immunohistochemistry (IHC). Patients received LORVIQUA orally at the recommended dose of 100 mg once daily, continuously.

The primary efficacy endpoint in the Phase 2 portion of the study was objective response rate (ORR), including intracranial ORR, as per Independent Central Review (ICR) according to modified Response Evaluation Criteria in Solid Tumours (modified RECIST version 1.1). Secondary endpoints included duration of response (DOR), intracranial DOR, time-to-tumour response (TTR), and progression-free survival (PFS).

Patient demographics of the 197 ALK-positive advanced NSCLC patients previously treated with 1 or more ALK TKIs, were 59% female, 49% Caucasian, 36% Asian and the mean age was

53 years (range: 29 to 85 65 years of age. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 or 1 in 97% of patients and 2 in 4% of patients.[70] Brain metastases were present at baseline in 67% of patients. All 197 patients had received prior systemic therapy, 20% received 1, 28% received 2, 19% received 3 and 34% received 4 or more prior systemic therapies. Of the 197 patients, 44% received 1 prior ALK TKI, 33% received 2 prior ALK TKIs, and 23% received 3 or more prior ALK TKIs.

The main efficacy results for Study B7461001 are included in Tables 3 and 4.

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

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

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

[a] Alectinib, brigatinib, or ceritinib.

[b] Per ICR.

[c] Using exact method based on binomial distribution.

[d] Using the Brookmeyer Crowley method.

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

	One 2nd generation ALK TKI[a] (N=12)	**2 or more ALK TKIs (N=83)**	**1 or more ALK TKIs (N=132)**
Objective response rate[b] (95% CI)[c]	41.7% (15.2, 72.3)	48.2% (37.1, 59.4)	53.0% (44.2, 61.8)
Complete response, n	1	24	35
Partial response, n	4	16	35
Duration of response Median, Months (95% CI)[d]	NR (4.1, NR)	14.5 (8.3, 14.5)	14.5 (NR, NR)

* In patients with at least 1 measurable baseline brain metastasis.

Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; ICR=Independent Central Review; N/n=number of patients; NSCLC=non-small cell lung cancer; NR=not reached; ORR=objective response rate; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

[a] Alectinib, brigatinib, or ceritinib.

[b] Per ICR.

[c] Using exact method based on binomial distribution.

[d] Using the Brookmeyer Crowley method.

Among the 93 patients with a confirmed objective response by ICR, the median TTR was 1.4 months (range: 1.1 to 11.0 months). Among the 70 patients with a confirmed objective tumour response by ICR, the median intracranial-TTR was 1.4 months (range: 1.1 to 6.2 months).

5.2 Pharmacokinetic properties

Absorption

Peak lorlatinib concentrations in plasma are rapidly reached with the median T_{max} of 1.2 hours following a single 100 mg dose and 2.0 hours following 100 mg once daily multiple dosing.

After oral administration of LORVIQUA, the mean absolute bioavailability is 80.8% (90% CI: 75.7%, 86.2%) compared to intravenous administration.

Administration of lorlatinib with a high fat, high calorie meal resulted in 5% higher exposure compared to overnight fasting (AUC_{inf} ratio of 104.7%; 90% CI for the ratio: 101.3%, 108.3%). LORVIQUA may be administered with or without food. The proton-pump inhibitor rabeprazole had a minimal effect on lorlatinib plasma exposure (AUC_{inf} ratio of 100.9%; 90% CI for the ratio: 97.6%, 104.3%). No dose adjustment is recommended when LORVIQUA is taken with proton-pump inhibitors, H_2-receptor antagonists or locally acting antacids.

The steady-state systemic exposure (C_{max} and AUC_{24}) increased less than proportionally over a lorlatinib dosing range of 10 to 200 mg once daily. At the 100 mg once daily lorlatinib dose, the geometric mean peak plasma concentration was 577 ng/mL and the AUC_{24} 5650 patients with cancer. The geometric mean oral clearance was 17.7 L/h. Lorlatinib oral clearance increased at steady-state compared to single dose, indicating autoinduction.

Distribution

In vitro binding of lorlatinib to human plasma proteins is 66% with moderate binding to albumin and low binding $_1$-acid glycoprotein.

Metabolism

In humans, lorlatinib undergoes oxidation and glucuronidation as the primary metabolic pathways. *In vitro* data indicate that lorlatinib is metabolized primarily by CYP3A4 and UGT1A4, with minor contribution from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.

In plasma, a benzoic acid metabolite (M8) of lorlatinib resulting from the oxidative cleavage of the amide and aromatic ether bonds of lorlatinib was observed as a major metabolite, accounting for 21% of the circulating radioactivity. The oxidative cleavage metabolite is pharmacologically inactive.

Elimination

The plasma half-life of lorlatinib after a single 100 mg dose was 23.6 hours. Following oral administration of a 100 mg radiolabeled dose of lorlatinib, a mean 47.7% of the radioactivity was recovered in urine and 40.9% of the radioactivity was recovered in 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 in plasma and faeces, respectively. Less than 1% of unchanged lorlatinib was detected in urine.

Cardiac electrophysiology

QT interval

In Study B7461001, 2 patients (0.7%) had absolute Fridericia's correction QTc (QTcF) values >500 msec, and 5 patients (1.8%) had a change in QTcF from baseline >60 msec.

In addition, the effect of a single oral dose of lorlatinib (50 mg, 75 mg, and 100 mg) with and without 200 mg once daily itraconazole was evaluated in a 2-way crossover study in 16 healthy volunteers. No increases in the mean QTc interval were observed at the mean observed lorlatinib concentrations in this study.

In 295 patients who received lorlatinib at the recommended dose of 100 mg once daily in Study B7461001, no large mean increases from baseline in the QTcF interval (i.e. >20 ms) were detected.

PR interval

In 295 patients who received lorlatinib at the recommended dose of 100 mg once daily and had a ECG measurement in Study B7461001, the maximum mean change from baseline for PR interval was 16.4 ms (2-sided 90% upper CI: 19.4 ms). Among the 284 patients with PR interval <200 ms, 14% had PR ms after starting lorlatinib. The prolongation of PR interval occurred in a concentration-dependent manner. Atrioventricular block occurred in 1.0% of patients.

For those patients who develop PR prolongation, dose modification may be required (see Section 4.2).

Special populations

Hepatic impairment

As lorlatinib is metabolized in the liver, hepatic impairment is likely to increase lorlatinib plasma concentrations. Clinical studies that were conducted excluded patients with AST or ALT >2.5 × ULN, or if due to underlying malignancy, >5.0 × ULN or with total bilirubin >1.5 × ULN. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild hepatic impairment (n=50). No dose adjustments are recommended for patients with mild hepatic impairment (see Section 4.2). Lorlatinib has not been studied in patients with moderate or severe hepatic impairment.

Renal impairment

Less than 1% of the administered dose is detected as unchanged lorlatinib in urine. Clinical studies excluded patients with serum creatinine >1.5 × ULN or estimated CL_{cr} <60 mL/min. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild (n=103) or moderate (n=41) renal impairment

(CL_{cr} ³ 30 mL/min). No dose adjustments are recommended for patients with mild or moderate renal impairment (see Section 4.2). Information for lorlatinib use in patients with severe renal impairment (CL_{cr} <30 mL/min) is limited (n=1).

Elderly (³65 years)

Of the 295 patients in safety population in Study B7461001, 18.3% of patients were aged 65 years or older. Of the 215 patients in the efficacy population in Study B7461001, 17.7% of patients were aged 65 years or older. Although data are limited, no clinically relevant differences in safety or efficacy were observed between patients aged greater than or equal to 65 years and younger patients; no dose adjustments are recommended in elderly patients (see Section 4.2).

Gender, race, body weight, and phenotype

Population pharmacokinetic analyses in patients with advanced NSCLC and healthy volunteers indicate that there are no clinically relevant effects of age, gender, race, body weight, or phenotypes for CYP3A5 and CYP2C19.

5.3 Preclinical safety data

Repeat-dose toxicity

The main toxicities observed were inflammation across multiple tissues (with increases in white blood cells), and changes in the pancreas (with increases in amylase and lipase), hepatobiliary system (with increases in liver enzymes), male reproductive system, cardiovascular system, kidneys and gastrointestinal tract, and peripheral nerves and the central nervous system (potential for cognitive functional impairment) (observed at as low as the human clinical exposure at 100 mg based on AUC for all toxicities). Changes in blood pressure and heart rate, and QRS and PR interval prolongation were also observed in animals after acute dosing (approximately 2.6 times the human clinical exposure at 100 mg after a single dose based on C_{max}). All target organ findings with the exception of the hepatic bile duct hyperplasia were partially to fully reversible.

Genotoxicity

Lorlatinib was not mutagenic in a bacterial reverse mutation (Ames) assay. Lorlatinib induced micronuclei via an aneugenic mechanism in human lymphoblastoid TK6 cells *in vitro* and in the bone marrow of rats.

Carcinogenicity

Carcinogenicity studies have not been conducted with lorlatinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core contains:
Microcrystalline cellulose
Calcium hydrogen phosphate
Sodium starch glycollate
Magnesium stearate

Film-coating contains:
Hypromellose (E464)
Lactose monohydrate
Macrogol 3350
Triacetin
Titanium dioxide (E171)
Iron oxide black (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

Aluminium foil blisters with aluminium foil backing containing 10 film-coated tablets.
Pack sizes:
25 mg: 9 blister strips (90 tablets) per carton.
12 blister strips (120 tablets) per carton.
100 mg: 3 blister strips (30 tablets) per carton.

HDPE bottles with a polypropylene child resistant closure and desiccant canister. Each bottle contains 30 tablets.

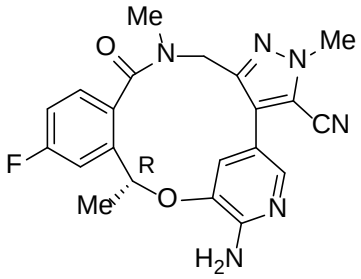
Not all presentations may be marketed.

6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure



CAS number: 1454846-35-5

Molecular weight: 406.4
Aqueous solubility: decreases over the range pH 2.55 to pH 8.02 from 32.38 mg/mL to 0.17 mg/mL.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8. SPONSOR

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9. DATE OF FIRST APPROVAL

19 November 2019

10. DATE OF REVISION

Not applicable

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