Indication	Monotherapy for the treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced (stage IIIb or IV) non-small cell lung cancer (NSCLC) whose disease has progressed after: • 1st line alectinib or 1st line ceritinib or 1st line brigatinib; or • 1st line crizotinib followed by a 2nd line ALK tyrosine kinase inhibitor therapy (brigatinib or ceritinib) or after disease progression during adjuvant alectinib or within 6 months of completion of adjuvant alectinib.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days. Continue until disease progression or excessive toxicity or patient choice to discontinue treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • FBC, LFTs and U&Es baseline and at each cycle. • Monitoring of serum cholesterol and triglycerides should be done before treatment, on day 14 of cycle 1 and then before each cycle. Frequency of monitoring of cholesterol and triglycerides may be reduced from cycle 4 at clinician discretion, if indicated. Where appropriate initiate or increase the dose of lipid-lowering medicinal products. • Patients should be monitored for lipase and amylase elevations prior to the start of treatment and regularly thereafter as clinically indicated. • Fasting serum glucose before treatment and throughout treatment. Dose interruption/modification maybe required see table 1. • **ECG** prior to treatment and at each cycle thereafter. • 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. • **BP** before treatment, on day 14 of cycle 1 and at each cycle thereafter. Dose interruption/modification maybe required see table 1. • Confirm the patient either has no brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting lorlatinib. • **Hepatic Impairment:** No dose adjustments are recommended for patients with mild hepatic impairment. No data is available to make a recommendation in patients with moderate or severe hepatic impairment (AST / ALT >2.5 x ULN, or if due to malignancy >5.0 x ULN or with bilirubin > 1.5 × ULN). • **Renal Impairment:** No dose adjustment required in mild or moderate (CrCl >/= 30ml/min) renal impairment. A reduced starting dose of 75mg OD is recommended in patients with severe renal impairment (absolute CrCl < 30 mL/min). No information is available for patients on renal dialysis. • **Dose modification and adverse reactions:**

	• Dosing interruption or dose reduction may be required based on individual safety and tolerability. 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. • See table 1 for dose modifications for adverse effects (including central nervous system (CNS) reactions, PR interval prolongation and AV block, interstitial lung disease (ILD)/Pneumonitis, Hypercholesterolaemia or hypertriglyceridaemia, Lipase/Amylase increase, hypertension and hyperglycaemia). • **Visual disturbance** adverse reactions have occurred in patients treated with lorlatinib. Patients should be advised to report any visual symptoms. For new or worsening severe visual symptoms, an ophthalmologic evaluation and dose reduction should be considered. • **Interstitial lung disease/Pneumonitis:** Severe and life threatening pulmonary adverse reactions have been reported including ILD/pneumonitis. Patients should be advised to report any new or worsening respiratory symptoms. If pneumonitis is suspected treatment should be withheld and/or permanently discontinued based on severity (see table 1). • **Common drug interactions: (for comprehensive list refer to BNF/SPC)** • Concurrent use with strong CYP3A4/5 inhibitors (eg ketoconazole, itraconazole, clarithromycin) should be avoided. If a strong CYP3A4/5 inhibitor must be • co-administered, the starting dose should be **reduced to 75 mg once daily**. 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. Grapefruit juice should be avoided. • Concomitant use with strong CYP3A4/5 inducers (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, St John's Wort) is contraindicated. Caution with CYP3A4/5 substrates with a narrow therapeutic index (e.g. Ciclosporin, fentanyl, tacrolimus, and hormonal contraceptives); the concentration of these medicinal products may be reduced by lorlatinib. • Lorlatinib should be used with caution with the following groups of medicines; CYP2C9, UGT and P-gp substrates. Patients should be closely monitored if receiving concomitant therapy with a narrow therapeutic index. • **Missed dose:** If a dose 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. • **Contraception:** A highly effective non-hormonal method of contraception should be used for female patients (see SPC and interactions), continuing until at least 35 days after completing treatment. Male patients with female partners who are of childbearing age or pregnant must use a condom and where applicable other contraceptives during treatment and for at least 14 weeks after last dose. • **Driving and Machinery:** Patients should be advised that lorlatinib can have an effect on their ability to drive and use machines. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	KMCC protocol LUN-044 V2 SPC accessed online 03.03.2024 CDF list V1.351 accessed online 03.03.2025

NB For funding information, refer to CDF and NICE Drugs Funding List

Protocol No	LUN-044	Kent and Medway SACT Protocol Disclaimer: No responsibility will be accepted for the accuracy of this information when used elsewhere.	
Version	V3	Written by	M.Archer
Supersedes version	V2	Checked by	C.Waters V3 E.Parry V2 V3 updated in line with SPC and commissioning criteria only.
Date	31.03.2025	Authorising consultant (usually NOG Chair)	T.Sevitt V2

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.
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 (comprises psychotic effects and changes in cognition, mood, mental state or speech)	
Grade 2: Moderate OR Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume lorlatinib at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.
Lipase/Amylase increase	
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at 1 reduced dose level.
Interstitial lung disease (ILD)/Pneumonitis	
Grade 1: Mild OR Grade 2: Moderate	Withhold lorlatinib until symptoms have returned to baseline and consider initiating corticosteroids. Resume lorlatinib at 1 reduced dose level. Permanently discontinue lorlatinib if ILD/pneumonitis recurs or fails to recover after 6 weeks of lorlatinib hold and steroid treatment.
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.
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.

PR interval prolongation/Atrioventricular (AV) block (continued)	
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.
Hypertension	
Grade 3 (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg; medical intervention indicated; more than one antihypertensive drug, or more intensive therapy than previously used indicated)	Withhold lorlatinib until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume lorlatinib at the same dose. If Grade 3 hypertension recurs, withhold lorlatinib until recovery to Grade 1 or less, and resume at a reduced dose. If adequate hypertension control cannot be achieved with optimal medical management, permanently discontinue lorlatinib.
Grade 4 (Life-threatening consequences, urgent intervention indicated)	Withhold lorlatinib until recovery to Grade 1 or less, and resume at a reduced dose or permanently discontinue lorlatinib. If Grade 4 hypertension recurs, permanently discontinue lorlatinib.
Hyperglycaemia	
Grade 3 (greater than 250 mg/dL despite optimal anti-hyperglycaemic therapy) OR Grade 4	Withhold lorlatinib until hyperglycaemia is adequately controlled, then resume lorlatinib at the next lower dose. If adequate hyperglycaemic control cannot be achieved with optimal medical management, permanently discontinue lorlatinib.
Other adverse reactions	
Grade 1: Mild OR Grade 2: Moderate	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3: Severe	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib at 1 reduced dose level.
[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.	

Repeat every 28 days.

TTO	Drug	Dose	Route	Directions
Day 1	**LORLATINIB**	**100mg**	**PO**	OD at the same time every day. The tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Avoid grapefruit juice. Available as **25mg** and **100mg** tablets. Dispense 30 days supply
	Metoclopramide	10mg	PO	10mg up to three times a day PRN. Do not take for more than 5 days continuously. Dispense on Cycle 1 only, then only as required.
	Loperamide	2mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 only, then only as required.