Lorlatinib

Indication

Treatment of anaplastic lymphoma kinase (ALK) positive advanced or metastatic non-small cell lung cancer (NSCLC) in adults whose disease has progressed after:

- 1st line alectinib, ceritinib or brigatinib; or
- 1st line crizotinib followed by a 2nd line ALK tyrosine kinase inhibitor therapy (brigatinib or ceritinib)

(NICE TA628)

Treatment of ALK-positive advanced non-small-cell lung cancer not previously treated with an ALK inhibitor.

(NICE TA1103)

ICD-10 codes

Codes with a prefix C34

Regimen details

Day	Drug	Dose	Route
1-28	Lorlatinib	100mg OD	PO

Cycle frequency

28 days

Number of cycles

Continue until disease progression or unacceptable toxicity.

Administration

Lorlatinib is available as 100mg and 25mg tablets.

The tablets should be taken whole, with or without food, at around the same time each day. 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 omit the missed dose.

Grapefruit and grapefruit juice should be **avoided** whilst taking lorlatinib.

Pre-medication

Nil

Emetogenicity

This regimen has low emetic potential (no routine antiemetics required)

Additional supportive medication

Nil

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Cholesterol	14 days
Triglycerides	14 days
Lipase	14 days
Amylase	14 days
Glucose	14 days
ECG	28 days

Consider echocardiogram for baseline LVEF assessment in patients with cardiac risk factors or with conditions that can affect LVEF.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local practice)
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Cholesterol*	7 days
Triglycerides*	7 days
Lipase**	7 days
Amylase**	7 days
Glucose**	7 days

ECG should also be monitored monthly for the first 3 months and regularly thereafter, particularly in patients with cardiac risk factors.

Consider monitoring of LVEF with regular echocardiogram in patients with baseline LV impairment, cardiac risk factors or who develop cardiac symptoms / signs during treatment

*Serum cholesterol and triglycerides should be monitored 2, 4 and 8 weeks after initiating lorlatinib; and regularly thereafter.

**Patients should be monitored for lipase and amylase elevations and hyperglycaemia regularly as clinically indicated.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/consultant.

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	≥ 30mL/min
AST/ALT	< 2.5 x ULN (<5 x ULN if due to malignancy)
Bilirubin	< 1.5 x ULN
Cholesterol	< 12.9 mmol/L
Triglycerides	< 11.4 mmol/L
Lipase	< 2 x ULN if signs/symptoms; < 5 x ULN asymptomatic
Amylase	< 2 x ULN if signs/symptoms; < 5 x ULN asymptomatic

Dose modifications

Dose level	Dose
Full dose	100mg OD
First dose reduction	75mg OD
Second dose reduction	50mg OD

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

- **Haematological toxicity**

No information on dose modifications is available. If neutrophils < 1.0 x 10^9/L or platelets <50 x 10^9/L discuss with consultant.

- **Renal impairment**

In patients with severe renal impairment (CrCl < 30mL/min) it is recommended to start lorlatinib at a reduced dose e.g. 75mg OD with close monitoring.

- **Hepatic impairment**

As lorlatinib is metabolised in the liver, hepatic impairment is likely to increase lorlatinib plasma concentrations.

No dose adjustment is recommended for patients with mild hepatic impairment but lorlatinib is not recommended in patients with moderate to severe hepatic impairment due to lack of information. Clinical studies 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.

- **Other toxicities**

Hypercholesterolaemia or Hypertriglyceridaemia

Cholesterol		Triglycerides	Action
Mild-moderate hypercholesterolaemia (cholesterol >ULN - 10.3 mmol/L)	**OR**	Mild-moderate hypertriglyceridaemia (triglycerides between 1.7 and 5.7 mmol/L)	Introduce or modify lipid-lowering therapy* Continue lorlatinib at the same dose.
Severe hypercholesterolaemia (cholesterol 10.3 - 12.9 mmol/L)	**OR**	Severe hypertriglyceridaemia (triglycerides between 5.7 and 11.4 mmol/L)	Introduce or increase lipid-lowering therapy* Continue lorlatinib at the same dose without interruption.
Life-threatening hypercholesterolaemia (cholesterol > 12.9 mmol/L)	**OR**	Life-threatening hypertriglyceridaemia (triglycerides over 11.4 mmol/L)	Introduce or increase lipid-lowering therapy* Withhold lorlatinib until recovery to moderate or mild severity grade. Re-challenge at same lorlatinib dose while maximising lipid-lowering therapy If severe toxicity recurs despite maximal lipid-lowering therapy, reduce lorlatinib by 1 dose level.

*Pravastatin is preferred as it has the least potential for interaction with lorlatinib

Central Nervous System effects

Includes psychotic effects and changes in cognition, mood, mental state or speech

Grade	Action
Grade 2 or 3	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

Lipase/Amylase	Action
> 2 x ULN if signs/symptoms ***OR*** > 5 x ULN if asymptomatic	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at 1 reduced dose level.

Interstitial Lung Disease/Pneumonitis

Grade	Action
Grade 1 or 2	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 or 4	Permanently discontinue lorlatinib.

PR interval prolongation/Atrioventricular (AV) block

Consider concomitant medicines, and assess and correct electrolyte imbalance

AV Block		Action
First degree AV block	Asymptomatic	Continue lorlatinib at the same dose without interruption
	Symptomatic	Withhold lorlatinib. If symptoms resolve, resume lorlatinib at 1 reduced dose level
Second degree AV block	Asymptomatic	Withhold lorlatinib. If subsequent ECG does not show second degree AV block, resume lorlatinib at 1 reduced dose level.
	Symptomatic	Withhold lorlatinib. Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic AV block persists. If second-degree AV block resolves or if patients revert to asymptomatic first-degree AV block, resume lorlatinib at 1 reduced dose level.
Complete AV block	Withhold lorlatinib. 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.	

Other adverse reactions

Grade	Action
Grade 1 or 2	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
≥Grade 3	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib at 1 reduced dose level

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Pneumonitis
Anaemia
PR interval prolongation/Atrioventricular (AV) block

- **Frequently occurring side effects**

Hyperlipidaemia
Oedema
Peripheral neuropathy
Cognitive effects
Fatigue
Weight increase
Arthralgia/Myalgia
Mood effects
Diarrhoea/Constipation
Nausea
Rash
Visual disturbances

- **Other side effects**

Headache
Speech effects
Lipase increase
Amylase increase

Significant drug interactions – for full details consult product literature/ reference texts

Coumarin anticoagulants, e.g. warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.
Medications which may cause AV block (e.g. beta blockers, calcium channel blockers, digoxin, other anti-arrhythmics)**:** use with caution and monitor closely (see above).
Strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin)**:** avoid co-administration as these may increase lorlatinib plasma concentrations. If a strong CYP3A4/5 inhibitor must be co-administered, the starting lorlatinib dose should be reduced to 75mg once daily.
Grapefruit juice products: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of lorlatinib.
Inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort)**:** avoid co-administration as these may reduce lorlatinib plasma concentrations.
CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, fentanyl, hormonal contraceptives, quinidine, sirolimus and tacrolimus)**:** avoid if possible since the concentration of these medicinal products may be reduced by lorlatinib.
P-glycoprotein substrates e.g. digoxin, dabigatran etexilate: use with caution as lorlatinib is a moderate inducer of P-gp so may cause reduced plasma concentrations of these agents.

Additional comments

As lorlatinib can render hormonal contraceptives ineffective, a highly effective non-hormonal method of contraception is required for female patients during treatment and for at least 35 days after completing therapy. Male patients with female partners of childbearing potential must use effective contraception during treatment and for at least 14 weeks after the final dose.

References

- Summary of Product Characteristics – Lorlatinib (Pfizer) accessed via www.medicines.org.uk (04 January 2021).
- National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance 628 accessed via www.nice.org.uk (04 January 2021).
- National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance 1103 accessed via www.nice.org.uk (13 November 2025).
- NHS England Cancer Drug Fund List via www.england.nhs.uk (04 January 2021).
- Solomon, B.J. et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study, Lancet Oncol. 19 (12) (2018) 1654–1667.
- Felip E et al. Intracranial and extracranial efficacy of lorlatinib in patients with ALK-positive non-small-cell lung cancer previously treated with second-generation ALK TKIs. Ann Oncol. 2021 Feb 24:S0923-7534(21)00129-0

Written/reviewed by: Dr N Cox (Clinical Oncology Registrar, UHBW NHS Trust), Dr G Ayre (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance)

Authorised by: Dr Jeremy Braybrooke (Consultant Oncologist, UHBW NHS Trust, SWAG Cancer Alliance)

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