Lorlatinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC), following disease progression on (i) alectinib or ceritinib as the first ALK-targeted treatment or (ii) crizotinib and at least one other ALK-targeted treatment	C34	00570a	CDS[i] 1/10/2019

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Lorlatinib is administered orally once daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Lorlatinib	100mg	PO	continuous
Missed Dose: If a dose is missed, the patient should make up that dose, unless the next dose is due within 4 hours Lorlatinib can be taken with or without food. The tablets should be swallowed whole and can be taken with or without food			

ELIGIBILTY:

- Indications as above
- ALK-positive NSCLC as demonstrated by an accurate and validated test method
- ECOG 0-2
- Adequate organ function as defined by

EXCLUSIONS:

- Hypersensitivity to lorlatinib or to any of the excipients
- Clinically significant interstitial fibrosis or pulmonary interstitial disease
- Clinically significant cardiovascular disease

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- ALK-positive NSCLC as demonstrated by an accurate and validated test method
- Lipid profile (Serum cholesterol and triglycerides)
- Coagulation
- FBC, renal and liver profile
- ECG
- Amylase and lipase levels

Regular tests:

- Lipid profile(Serum cholesterol and triglycerides) at 2,4 and 8 weeks and then as clinically appropriate
- FBC, renal and liver profile monthly
- ECG monthly or as clinically indicated
- Amylase and lipase levels monthly

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Lorlatinib dose reduction levels are summarised in table 1 below
- Any dose modification should be discussed with a Consultant.

Table 1: Dose level reductions for lorlatinib

Dose level	Lorlatinib
Recommended starting dose	100mg
First dose reduction	75mg
Second dose reduction	50mg
Third dose reduction	Discontinue

Renal and Hepatic Impairment:

Table 2: Dose modification of lorlatinib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dose adjustments are recommended for patients with mild or moderate renal impairment. Information for lorlatinib use in patients with severe renal impairment is very limited. Therefore, lorlatinib is not recommended in patients with severe renal 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

Management of adverse events:

Table 3: Recommended dose Modification of lorlatinib for Adverse Events

Adverse reactions[a]	Dose modification
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 1000mg/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 500mg/dL or over 12.92 mmol/L) OR Life-threatening hypertriglyceridaemia (triglycerides over 1000mg/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 informationreduce lorlatinib by one dose level.
Central nervous system effects (changes in cognition, mood or speech)	
Grade 2-3	Withhold dose until toxicity is less than or equal to Grade 1. Then resume lorlatinib at one reduced dose level.
Grade 4	Permanently discontinue lorlatinib.
Lipase/Amylase increase	
Grade ≥3	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at one reduced dose level.
Interstitial lung disease (ILD)/Pneumonitis	
Grade ≤2	Withhold lorlatinib until symptoms have returned to baseline and consider initiating corticosteroids. Resume lorlatinib at one 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	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 one 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 one 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 one 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 one reduced dose level only when symptoms resolve and PR interval is less than 200 msec.
Other adverse reactions	
Grade ≤2	Consider no dose modification or reduce by one 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 one 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	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: Not required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Lorlatinib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Hyperlipidaemia**: The use of lorlatinib has been associated with increases in serum cholesterol and triglycerides. 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
- **Central nervous system effects**: Central nervous system (CNS) effects have been observed in patients receiving lorlatinib, including changes in cognitive function, mood or speech. Dose modification or discontinuation may be required for those patients who develop CNS effects (s)
- **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. 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
- **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.. 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. 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
- **Interstitial lung disease/Pneumonitis**: Severe or life-threatening pulmonary adverse reactions consistent with ILD/pneumonitis have occurred with lorlatinib. Any patient who symptoms indicative of ILD/pneumonitis should be promptly evaluated and lorlatinib should be withheld and/or permanently discontinued based on severity
- **Fertility, pregnancy and lactation**: A highly effective non-hormonal method of contraception is required for female patients of child bearing potential during treatment with lorlatinib. 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. Lorlatinib is not recommended during pregnancy or for women of childbearing potential not using contraception. Lorlatinib should not be used during breast-feeding.

DRUG INTERACTIONS:

- Concomitant use of a strong CYP3A4/5 inducer is contraindicated. Concomitant use with moderate CYP3A4/5 inducers should be avoided, if possible, as they may also reduce lorlatinib plasma concentrations
- Concurrent administration of lorlatinib with CYP3A4/5 substrates with narrow therapeutic indices should be avoided since the concentration of these medicinal products may be reduced by lorlatinib
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Lorlatinib - L01XE44

REFERENCES:

1. Solomon, BJ et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018; 19: 1654–67
2. Lorvigua® Summary of Product Characteristics accessed September 2019 available at https://www.ema.europa.eu/en/documents/product-information/lorviqua-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	26/07/2019		Prof Maccon Keane
2	01/10/2019	Updated reimbursement status	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/