LORLATINIB (Lorviqua)

INDICATION (ICD10) C34

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (LOR1)

1. Lorlatinib monotherapy for anaplastic lymphoma kinase positive rearrangement locally advanced or metastatic non-small-cell lung cancer previously treated with 1st line alectinib or 1st line brigatinib or 1st line ceritinib, or 1st line crizotinib followed by a 2nd line ALK tyrosine kinase inhibitor therapy brigatinib or ceritinib. No brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting lorlatinib. PS 0, 1 or 2. (TA628)

REGIMEN

LORLATINIB 100mg orally daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Until disease progression. A formal medical review as to whether treatment with lorlatinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment. Review every 2-3 months by CT scan.

ADMINISTRATION

Available as 25mg and 100mg capsules
Swallowed whole with or without food.
Grapefruit and grapefruit juice should be avoided while on lorlatinib

ANTI-EMETICS

Minimal risk

CONCURRENT MEDICATION REQUIRED

Lorlatinib	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every 2 weeks for 3 cycles then every cycle
Lipids, amylase every 1-2 cycles
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Creatinine every cycle
Fasting glucose at initiation and periodically
ECG baseline
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Lorlatinib	Hyperlipidaemia CNS effects AV block LVEF decrease Lipase and amylase increase Interstitial lung disease / pneumonitis

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Lorlatinib	Strong CYP3A4/5 inducers eg rifampicin associated with increases in LFTs and contraindicated. Avoid use with moderate CYP3A inducers 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. Avoid grapefruit and Seville oranges

DOSE MODIFICATIONS
Non-haematological
Lorlatinib

Any patient with a grade 3 or 4 toxicity not controlled by optimum supportive care will require a dose reduction.

Level	Lorlatinib dose
Starting dose	100mg daily
First dose reduction	75mg daily
Second dose reduction	50mg daily
Unable to tolerate 50mg dose	Discontinue

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

Hyperglycaemia

Grade 3 (greater than 250mg/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.

Hypercholesterolaemia or hypertriglyceridaemia

Mild hypercholesterolaemia (cholesterol between ULN and 300mg/dL or between ULN and 7.75mmol/L) or moderate hypercholesterolaemia (cholesterol between 301 and 400mg/dL or between 7.76 and 10.34mmol/L) or mild hypertriglyceridaemia (triglycerides between 150 and 300mg/dL or 1.71 and 3.42mmol/L) or moderate hypertriglyceridaemia (triglycerides between 301 and 500mg/dL or 3.43 and 5.7mmol/L)	Introduce or modify lipid-lowering therapy in accordance with respective prescribing information; continue lorlatinib at same dose.
Severe hypercholesterolaemia (cholesterol between 401 and 500mg/dL or between 10.35 and 12.92mmol/L) or severe hypertriglyceridaemia (triglycerides between 501 and 1000mg/dL or 5.71 and 11.4mmol/L)	Introduce the use of lipid-lowering therapy if currently on lipid-lowering therapy, increase the dose of this therapy in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue lorlatinib at the same dose without interruption.
Life-threatening hypercholesterolaemia (cholesterol over 500mg/dL or over 12.92mmol/L) or life-threatening hypertriglyceridaemia (triglycerides over 1000mg/dL or over 11.4mmol/L)	Introduce the use of lipid-lowering therapy or increase the dose of this therapy in accordance with respective prescribing information or change to a new lipid-lowering therapy. 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 in accordance with respective prescribing information. If severe hypercholesterolaemia and/or hypertriglyceridaemia recur despite maximal lipid-lowering therapy in accordance with respective prescribing information, reduce lorlatinib by 1 dose level.

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

Hypertension

Grade 3 (SBP greater than or equal to 160mmHg or DBP greater than or equal to 100mmHg; 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 140mmHg and DBP less than 90mmHg), 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.

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.

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.

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.

PR Interval prolongation/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, 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.

Hepatic impairment

Lorlatinib

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.

Renal impairment

Lorlatinib

No dose adjustment is needed for patients with normal renal function and mild or moderate (CrCl ≥30mL/min) renal impairment based on a population pharmacokinetic analysis. Information for lorlatinib use in patients with severe (CrCl <30mL/min) renal impairment is very limited therefore, lorlatinib is not recommended in patients with severe renal impairment.

REFERENCES

1. SPC January 2020
2. CDF list