Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2239

lorlatinib 25mg and 100mg film-coated tablets (Lorviqua®)

Pfizer Limited

7 February 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life process

lorlatinib (Lorviqua®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
- crizotinib and at least one other ALK TKI

In the relevant subgroup of a non-comparative phase I/II study of previously-treated patients with ALK-positive advanced NSCLC, lorlatinib was associated with an objective response rate of approximately 40%.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after:[1]

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
- crizotinib and at least one other ALK TKI

Dosing Information

The recommended dose is 100mg lorlatinib taken orally once daily.
Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity. Dosing interruption or dose reduction may be required based on individual safety and tolerability.
Patients should be encouraged to take their dose of lorlatinib at approximately the same time each day with or without food. The 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.
Treatment with lorlatinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.
Further details are included in the summary of product characteristics (SPC).[1]

Product availability date

August 2019
Lorlatinib has conditional marketing authorisation from the European Medicines Agency and meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Lorlatinib is a third-generation inhibitor of ALK and c-ros oncogene 1 (ROS1) tyrosine kinases. It crosses the blood-brain barrier and has broad-spectrum potency against multiple ALK kinase domain resistance mutations that can develop during treatment with existing first-generation and second-generation ALK tyrosine kinase inhibitors (TKIs).[1, 2]

The evidence for the efficacy and safety of lorlatinib for this indication comes from Study 1001, an exploratory non-comparative phase I/II study. The phase II part of this ongoing study is multicentre, open-label, single-arm and included adults with metastatic, stage IV, NSCLC (histologically or cytologically confirmed) that carried a locally determined ALK or ROS1 gene rearrangement. Patients were required to have ≥1 measurable target extracranial lesion as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Patients with asymptomatic central nervous system (CNS) metastases, with or without prior treatment, were permitted in the study. Patients were required to have adequate bone marrow, liver, pancreatic and renal function, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.[2, 3]

Patients were assigned to expansion cohorts (EXP) on the basis of their ALK or ROS1 mutation status and prior treatments for NSCLC (n=275). The expansion cohorts relevant to the indication under review are EXP-3B, 4 and 5:[2, 3]

- EXP-3B: ALK-positive patients with disease progression following one previous non-crizotinib ALK tyrosine kinase inhibitor with any number of chemotherapy regimens (n=28).
- EXP-4 and EXP-5: ALK-positive patients with disease progression following two (EXP-4) or three (EXP-5) previous ALK tyrosine kinase inhibitors with any number of chemotherapy regimens (n=65, n=46 respectively).

All patients received lorlatinib 100mg orally once daily continuously in 21-day cycles. Treatment continued until investigator-assessed disease progression, unacceptable toxicity, withdrawal of consent, or death. Treatment could continue after objective progression on treatment if in the investigator's opinion there was evidence of clinical benefit. Dose delays and reductions (to 75mg, 50mg and 25mg) were permitted to manage toxicities and patients requiring more than three dose reductions were discontinued from treatment.[2, 3]

The study had two co-primary outcomes: objective tumour response (defined as a confirmed complete response or partial response) and intracranial tumour response, both according to RECIST version 1.1. These outcomes were assessed by independent central review (ICR) in patients who received at least 1 dose of lorlatinib.[2, 3] Confirmed responses were those which were sustained on repeat imaging at least 4 weeks after the initial documentation of response.[2, 3] The study did not include formal hypothesis testing and all statistics are descriptive only. The analyses of the subgroup relevant to this submission, EXP-3B to 5, were conducted post hoc.

The results demonstrated an overall objective response rate (ORR) of 40% in the pooled study subgroups representing the licensed indication (EXP-3B to EXP-5). The intracranial response in this subgroup was 54%. The detailed results are described in Table 1.[3]

Table 1. Results of the updated analyses of the co-primary outcomes of Study 1001 based on independent committee review, data cutoff 02 February 2018.[3]

	EXP-3B	**EXP-4 and 5**	**EXP-3B to 5 (pooled)**
Overall responses	n=28	n=111	n=139
Confirmed objective response, (n) 95%CI	43% (12), 24 to 63%	40% (44), 30 to 49%	40% (56) 32 to 49%
Complete response, (n)	3.6% (1)	1.8% (2)	2.2% (3)
Partial response, (n)	39% (11)	38% (42)	38% (53)
Intracranial responses [A]	n=9	n=48	n=57
Confirmed objective response, (n) 95%CI	67% (6) 30 to 92%	52% (25) 37 to 67%	54% (31) 41 to 68%
Complete response, (n)	22% (2)	21% (10)	21% (12)
Partial response, (n)	44% (4)	31% (15)	33% (19)

[A]number of patients with at least one measurable CNS lesion at baseline. CI=confidence interval

An analysis of response disagreement between ICR and investigator assessment reported overall response disagreement rates of 19%, 23% and 13% for EXP-3, EXP-4 and EXP-5 respectively, with higher ICR response rates. The intracranial response disagreement rates, for the same groups were 27%, 29% and 25% respectively.[3]

The results of secondary outcomes were supportive of the co-primary outcomes. For the pooled EXP-3B to EXP-5 group median time to tumour response was the same (1.4 months) in the intracranial group and the overall group. Median duration of intracranial response was 12.4 months. The median duration of follow-up for overall survival for the pooled EXP-3B to EXP-5 group was approximately 20 months.[3] The detailed results for overall survival and progression-free survival are described in Table 2[3, 4]

Table 2. Results of the updated analyses of the secondary outcomes of Study 1001 based on independent committee review, data cutoff 02 February 2018[3, 4]

		EXP3B	EXP4-5	EXP3B to EXP5
		n=28	n=111	n=139
Progression-free survival	Number of patients with a PFS event	20	77	97
	median time to event, months (95%CI)	5.5 (2.9 to 8.2)	6.9 (5.4 to 9.5)	6.9 (5.4 to 8.2)
	Probability of being event-free at 12 month	27%	33%	32%
Overall survival	Number of deaths	*	*	*
	median time to event, months (95%CI)	21.1 months (12.3 to NR)	19.2 months (15.4 to NR)	*
	Survival probability at 12 month	70%	67%	*[4]

CI=confidence interval, NR=not reached

In the pooled EXP-3B to EXP-5 subgroup, lorlatinib demonstrated efficacy in patients previously treated with alectinib, brigatinib, ceritinib, crizotinib and chemotherapy.[3]

European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaires (EORTC-QLQ) C-30 and lung cancer (LC)-13 were used to evaluate health-related quality of life in patients treated with lorlatinib. The LC13 questionnaire evaluates 13 typical symptoms of lung cancer patients, including coughing, pain, dyspnoea, sore mouth, peripheral neuropathy, and hair loss.[5] For functioning, symptom and global quality of life (QoL) domains scores were categorised as improved, worsening or stable. For the Global QoL domain of QLQ-C30 approximately 43% of patients improved and 40% were stable during treatment. For both QLQ-C30 and LC13 a greater proportion of patients improved rather than worsened for most symptoms, with the exceptions of sore mouth, alopecia and peripheral neuropathy.[3]

The submitting company presented two unanchored matching adjusted indirect comparisons (MAICs) comparing lorlatinib with chemotherapy (including single-agent pemetrexed or docetaxel or unspecified), as a proxy for platinum doublet chemotherapy, in adult patients with ALK positive NSCLC whose disease had progressed following prior treatment with one or two ALK TKIs. Separate MAICs were conducted for progression free survival (PFS) and overall survival. Lorlatinib data from Study 1001 were compared with pooled chemotherapy PFS data from ALUR and ASCEND-5 (both phase III studies), and pooled overall survival data from PROFILE 1001/1005 (phase I/II).[6-8] Hazard ratios and 95% confidence intervals indicated statistically significant improvements associated with lorlatinib over chemotherapy for both outcomes. Sensitivity analyses produced results which were consistent with the base case analysis.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The EMA considered the adverse effect profile of lorlatinib 100mg to be tolerable and manageable.[3] The safety analysis set of both the phase I and II parts of Study 1001 included all patients who received at least one dose of lorlatinib 100mg, n=295. All patients reported at least one adverse event, almost all of these were considered treatment-related. The following treatment-related adverse events were reported: hypercholesterolemia (84%), hypertriglyceridemia (67%), oedema (55%), peripheral neuropathy (48%), fatigue (28%), cognitive effects (29%), weight gain (26%), mood effects (23%), diarrhoea (23%) and vision disorders (15%). The most common Grade 3 or 4 events were hypercholesterolemia/ hypertriglyceridemia.[3]

Lorlatinib may cause multiple CNS effects which could have a negative impact on the patient's quality of life.[3]

No comparative safety data are available for lorlatinib. Refer to the summary of product characteristics for details.[1, 3]

Summary of clinical effectiveness issues

Non-small cell lung cancer accounts for approximately 85 to 90% of lung cancers with ALK-positive NSCLC making up approximately 4 to 5% of NSCLC patients. Important prognostic factors for patients with ALK positive NSCLC include: nodal involvement, size of primary tumour, baseline pulmonary function, gender, presence or absence of significant weight loss, and performance status. The brain is a common site of metastases in ALK positive NSCLC and is associated with poor prognosis.[3] ALK-inhibitors are the main treatment options for ALK-positive advanced NSCLC with crizotinib (SMC1152/16) and alectinib (SMC2012) considered first-line options. Brigatinib (SMC2147) and ceritinib (SMC1097/15) are available for routine use for patients previously treated with crizotinib. Acquired treatment resistance may occur due to the emergence of bypass

resistance mechanisms which can lead to disease progression. Following these routinely available TKIs, platinum doublet chemotherapy is the standard of care, however benefits are modest and there is limited effect on intracranial metastases (objective response rate of approximately 21% in patients with intracranial metastases).[2, 3, 9, 10] Studies in patients receiving chemotherapy following progression on crizotinib have reported survival estimates ranging from 5.4 to 20 months.[7, 8] Lorlatinib therefore meets SMC end of life criteria for this indication. Clinical experts consulted by SMC considered that there is unmet need for a further targeted therapy for patients who progress on available TKIs.

The key strengths and uncertainties of the clinical evidence are summarised below:

Key strengths

- The results for Study 1001 co-primary outcomes, based on independent central review, demonstrated an overall objective response rate of 40% (56/139) in the study subgroup matching the licensed indication (EXP-3B to 5). The intracranial response in patients with at least one CNS lesion at baseline in this subgroup was 54% (31/57) which indicates good CNS penetration.
- Secondary outcomes describe a median PFS of 6.9 months and a median overall survival of approximately 20 months for patients treated with lorlatinib.[3]
- The EMA considered that the benefit of lorlatinib following disease progression on other ALK inhibitors in terms of ORR, PFS and overall survival, as clinically relevant and the stabilisation of CNS disease as highly clinically relevant in this patient population.[3]

Key uncertainties

- Study 1001 is a single arm study, and so no comparative data are available. The magnitude of any treatment effect is unknown in the absence of a control group.
- The key limitations of the MAICs are: the populations treated with chemotherapy are different to the population under review as crizotinib was the only prior ALK TKI; there is a lack of data on the use of platinum doublet chemotherapy in patients previously treated with an ALK TKI; the MAIC only matched the unanchored populations for four factors, therefore it is very likely that there is confounding from unmatched prognostic factors and effect modifiers; subsequent lines of treatment may confound overall survival.
- In the absence of randomisation and blinding Study 1001 is at high risk of selection bias for all outcomes; performance and detection bias for subjective patient reported outcomes such as those on health-related quality of life and safety outcomes.[3]
- There was a high response disagreement rate for ORR, up to 23%, between independent central review and study investigators. The EMA noted that these differences are likely to compromise the robustness of data.[3]
- The sample size for the Study 1001 subgroup relevant to the indication under review was limited (n=139). The subgroup of patients with disease progression following one previous non-crizotinib ALK TKI (EXP-3B) was particularly small (n=28) and accounted for 20% of recruited patients. Additionally, it is uncertain if Study 1001 results are likely to represent

results in the Scottish population: approximately 38% of patients were Asian, only 4% had an ECOG performance status of 2 and smoking status was not recorded.

Lorlatinib has an EMA conditional marketing authorisation. To further support efficacy in the second-line setting the company has a specific obligation to conduct a prospective single arm efficacy study investigating patients who progressed after alectinib or ceritinib as the first-line ALK-TKI therapy. SMC considered that this obligation would address important uncertainties in the clinical evidence presented.

The introduction of lorlatinib would offer patients an oral alternative to intravenous chemotherapy. Clinical experts consulted by SMC considered lorlatinib to be a therapeutic advancement as it offered a further targeted therapy and has better CNS penetration than standard chemotherapy.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of lorlatinib, as an end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- ALK-positive advanced NSCLC is an incurable, life-limiting condition and typically affects younger patients, who were previously well and usually have never smoked. There is a significant burden of symptoms including shortness of breath, cough, pain and fatigue. There is a high incidence of CNS metastases. This impacts on patients' ability to self-care, live independently, drive, and work. Patients are likely to have negative psychological effects relating to their diagnosis and their condition significantly impacts on their quality of life.

- There is clear unmet need for patients with ALK-positive advanced NSCLC. Current second or third line treatment is usually cytotoxic chemotherapy, which has limited efficacy and is associated with significant toxicity. In addition, the current treatment options have limited CNS penetration and control.

- Lorlatinib has demonstrated disease control in patients with ALK-positive advanced NSCLC, and in particular it has shown rapid intracranial disease control which is extremely relevant for patients with a high risk of CNS metastases. Lorlatinib may potentially increase overall survival. The high CNS response rate and control of symptoms would help patients to maintain independence, continue to work, drive, and participate in family activities. In patients who respond, treatment is likely to have positive psychological effect and maintain quality of life. Treatment with lorlatinib would also potentially extend the time before patients have to start chemotherapy, which is important to patients.

- If patients respond to treatment and symptoms are controlled, this would result in less care responsibilities for family/carers, reduced time of work, and less financial implications.
- Lorlatinib is a well-tolerated oral treatment and requires a 4-weekly outpatient appointment, rather than multiple visits for chemotherapy. Lorlatinib is expected to have fewer adverse events than chemotherapy and patients who have received lorlatinib noted that side effects were manageable. No significant service implications would be expected.

Additional Patient and Carer Involvement

We received patient group submissions from ALK Positive Lung Cancer UK and the Roy Castle Lung Cancer Foundation, which are both registered charities. ALK Positive Lung Cancer UK has not received any pharmaceutical company funding in the past two years. The Roy Castle Lung Cancer Foundation has received 7.5% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing lorlatinib to platinum doublet chemotherapy (carboplatin/cisplatin plus pemetrexed) for the treatment of adult patients with ALK positive NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy or following crizotinib and at least one other ALK TKI. SMC clinical expert feedback was that platinum doublet chemotherapy is a relevant comparator.

The economic analysis used a partitioned survival model with three health states (pre-progression, post-progression and death). The model used a 30-day cycle with half cycle correction applied, and adopted a lifetime horizon of 20 years, with patients entering the model at a mean age of 52.5 years.

The clinical data for lorlatinib were taken from the single-arm phase II Study 1001, which informed the patient baseline characteristics (age, weight, gender), PFS and overall survival for lorlatinib, treatment duration, utilities for progression-free survival for lorlatinib, and adverse events for the economic model. The relevant clinical studies identified for the treatment effect parameters for platinum doublet chemotherapy included: ALUR, ASCEND-5, and PROFILE 1001/1005. These studies were in single agent and unspecified chemotherapy, and used as a proxy for platinum doublet chemotherapy. ALUR and ASCEND-5 were used to provide evidence for PFS while a retrospective analysis of PROFILE 1001/1005 was used for overall survival estimates for platinum doublet therapy.

As no comparative data were available from the key study for lorlatinib, indirect treatment comparisons (ITCs) were required to enable a comparison with the platinum doublet

chemotherapy proxy comparator evidence. The base case used a naïve comparison involving the fitting of independent parametric functions to the observed lorlatinib and chemotherapy data for PFS and overall survival independently.

For overall survival and PFS the generalized Gamma function was selected for estimation of long-term lorlatinib outcomes while overall survival and PFS for double platinum chemotherapy applied the log-logistic function. Alternative approaches such as matching adjusted indirect treatment comparisons (MAICs) and naïve unadjusted hazard ratios derived from a Cox proportional hazards model were applied in scenario analyses.

Time on treatment (ToT) for lorlatinib was assumed to be the same as PFS with some adjustment to account for progressed patients who continue to receive lorlatinib for a period of time when newly progressed. Treatment duration for platinum doublet chemotherapy was assumed the same as PFS or a maximum of 6 cycles.

Age-adjusted treatment-specific utility values were used for the progression-free health state. For lorlatinib the values were derived from mapping EORTC QLQ-30 data collected within the phase II part of Study 1001 to the EQ-5D-3L based on a published algorithm. For doublet chemotherapy, a value of 0.72 was used, derived from the PROFILE 1014 study of crizotinib versus platinum-based chemotherapy. Post-progression utility was based on published sources, and in the base case estimated to be 0.65. Disutilities for selected treatment specific adverse events were not included in the main analysis due to the assumption that health-related quality of life from the clinical trials would account for this.

Costs included medicine acquisition, medicine administration, health state monitoring, concomitant medication, subsequent therapies, treatment of adverse events, and terminal care. Resource use for routine follow-up care associated with health states were sourced from previous health technology assessments.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price.

In the base case for lorlatinib versus platinum doublet chemotherapy the incremental cost-effectiveness ratio (ICER) is estimated at £38,209 per quality adjusted life year (QALY) with the PAS applied. The main driver of increased costs was additional medicine acquisition costs for lorlatinib compared to platinum doublet chemotherapy.

Table 3: Base case results lorlatinib versus platinum doublet chemotherapy at PAS prices

Treatment	ICER (cost/QALY)
Lorlatinib versus chemotherapy	£38,209

A range of scenario analyses were performed, the potentially most plausible scenarios presented in Table 4. In addition, scenario analysis was provided using the MAIC for the estimation of relative survival outcomes and this had the greatest upward impact on the ICER. This increased the ICER to £44,769 and the impact of using this as an alternative base case analysis for associated sensitivity analysis is shown in table 5.

Table 4: Selected scenario analysis results (lorlatinib versus platinum doublet chemotherapy) at PAS price

	Scenario Analysis	ICER (with PAS)
1	OS extrapolation: Exponential curve	£40,605
2	PFS extrapolation: Gompertz	£42,408
3	Treatment waning applied to the MAIC at 5 years	£38,980
4	Treatment waning applied to the MAIC at 3 years	£42,198
5	10 year time horizon	£36,729
6	Same utilities for PFS for lorlatinib and comparator (based on study 1001 values)	£38,866
7	Zhou et al.[11] utility of 0.59 for progressive disease applied to both treatment arms	£39,537
8	PDC ToT cap at 4 cycles	£38,291
9	Assuming ~50% increase in the assumed duration of treatment beyond progression	£41,287

ICER = incremental cost effectiveness ratio, OS = overall survival, PAS = patient access scheme, PDC = platinum doublet chemotherapy, PFS = progression-free survival, QALY = quality-adjusted life year, ToT = time on treatment.

Table *5*: Scenario analysis for MAIC (population 3B:5) analysis

	Scenario Analysis	ICER (with PAS)
	Base case: MAIC (using EXP-3B:5 data) for OS and PFS	£44,769
1	Treatment waning (hazard ratio = 1) applied to the MAIC (OS and PFS) at 5 years	£46,684
2	Treatment waning (hazard ratio = 1) applied to the MAIC (OS and PFS) at 3 years	£52,246
3	10 year time horizon	£43,520
4	Same utilities for PFS for lorlatinib and comparator (based on study 1001 values)	£45,597
5	Zhou et al.[11] utility of 0.59 for progressive disease applied to both treatment arms	£45,772
6	PDC ToT cap at 4 cycles	£44,884

7	OS HR=2 (applied to base data)	£88,396
8	OS HR=0.5 (applied to base data)	£37,988
9	Applying a HR=0.8 to the comparator arm	£49,762

The economic analysis was associated with a number of weaknesses and uncertainties:

- The main clinical evidence for lorlatinib is based on a single-arm, phase II study with small patient numbers, PFS and overall survival as secondary outcomes, and relatively immature overall survival data. As a consequence, the estimates of duration of treatment effect and overall survival and its extrapolation in the economic analysis are uncertain.
- Due to the limitations in the lorlatinib data, and especially in the comparator effectiveness evidence there is high uncertainty with the relative PFS and overall survival effectiveness of lorlatinib versus platinum doublet chemotherapy. The comparator evidence is based on chemotherapy data that may not match the effectiveness of platinum doublet chemotherapy, different sources were used for estimation of PFS and overall survival outcomes, and the evidence base for overall survival outcomes was particularly limited, based on retrospective data analysis of systemic therapy (presumed to be chemotherapy).
- The base case approach consisted of a naïve comparison of lorlatinib and comparator chemotherapy with independent curves fitted to each dataset. Compared to a naïve comparison, the MAICs performed have the advantage of adjusting for differences in patient characteristics but were only provided as scenario analyses. Using this approach assumes proportional hazards, which may not apply for the overall survival estimates. However, using the MAIC results for PFS and overall survival in the economic analysis with EXP-3B to 5 data resulted in an increased ICER £44,769, although there were limitations with the MAICs, as have been described above, including the weaknesses in the comparator data. The resulting hazard ratios indicated a benefit for lorlatinib.
- Despite the limitations of the MAICs the results from this approach can be considered just as or potentially more reliable as the base case naïve comparison. Due to high uncertainty in the overall survival estimates for lorlatinib versus the comparator with this approach, the company provided additional scenario analysis on request exploring the impact of variation in the overall survival hazard ratio on the ICER. While the variations were exploratory they did show sensitivity on the ICER, particularly when the hazard ratio was increased.
- Applying a treatment waning effect for lorlatinib when using relative effectiveness based on the ITCs/MAICs, assuming no treatment benefit for lorlatinib compared to platinum doublet chemotherapy (Hazard ratio = 1) from year 3 and from year 5 increased the ICER (see Tables 4 and 5).
- There is uncertainty over time on treatment estimates for lorlatinib (none of the parametric functions fitted to the data produced plausible estimates) so it had to be assumed that ToT was equal to PFS which itself is uncertain. Hence the company included some additional costs of treatment with lorlatinib to account for treatment beyond progression. Exploring this in scenario analysis to increase the assumed duration by ~50% increased the ICER to £41,287 (table 4).
- There were some limitations in the utility analysis which required mapping of health related quality of life data to the EQ-5D and also utility values from published literature, with

uncertainty explored in scenario analysis using alternative sources for utilities. ICER results are moderately sensitive to scenarios varying utilities, particularly for progressive disease which increased the ICER to £55,839/QALY when applying a lower utility of 0.59 for post-progression from Zhou et al.[11] (see Table 4).

After considering all the available evidence and the output from the PACE process, the Committee accepted lorlatinib for use in NHSScotland subject to ongoing evaluation and future reassessment.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence published 'Lung cancer: diagnosis and management' in 2019. For patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after first-line treatment with alectinib or ceritinib or after first-line treatment with crizotinib, followed by second-line treatment with ceritinib or brigatinib, these guidelines recommend pemetrexed with carboplatin or other platinum doublet chemotherapy.[9]

The European Society for Medical Oncology (ESMO) published 'Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up' in 2018. These guidelines recommend lorlatinib, brigatinib and platinum-based chemotherapy regimens as treatment option for patients who have progressed after a second or further lines of treatment with ALK TKIs; ceritinib, crizotinib, alectinib or brigatinib.[10]
The Scottish Intercollegiate Guidelines Network (SIGN) clinical guideline for the management of lung cancer (2014) does not make any recommendations for the treatment of advanced ALK-positive disease.[12]

Additional information: comparators

Platinum doublet chemotherapy: cisplatin or carboplatin plus pemetrexed or docetaxel, single agent chemotherapy: pemetrexed or docetaxel.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per 21 day cycle (£)
lorlatinib	**100mg oral once daily, continuous**	**3,698**
platinum doublet chemotherapy	carboplatin AUC 5 mg/ml/min intravenously on day 1 of each 21 day cycle for up to 4 cycles or cisplatin 75mg/m^2 intravenously on day 1 of each 21 day cycle for up to 4 cycles plus pemetrexed 500mg/m^2 intravenously on day 1 of each 21 day cycle, for up to 4 cycles or docetaxel 75mg/m^2 intravenously on day 1 of each 21 day cycle, for up to 4 cycles.	254 to 1,189
pemetrexed	500mg/m^2 intravenously on day 1 of each 21 day cycle, for up to 4 cycles	900
docetaxel	75mg/m^2 intravenously on day 1 of each 21 day cycle, for up to 4 cycles.	96

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online and BNF online 11.11.2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Doses calculated based on bodyweight of 70kg and body surface area of 1.8m^2. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated that there would be 52 patients eligible for treatment with lorlatinib each year and that 10 patients would receive treatment in year 1 rising to 31 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. Pfizer Limited. Lorlatinib (Lorviqua®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated: 27/08/19.
2. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR*, et al.* Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol. 2018;19(12):1654-67.
3. The European Medicines Agency (EMA) European Public Assessment Report. Lorlatinib (Lorviqua®). 28/02/2019, EMEA/H/C/004646/0000. Available at: www.ema.europa.eu
4. *Commercial in Confidence**.
5. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. European Journal of Cancer. 1994;30(5):635-42.
6. Novello S, Mazieres J, Oh IJ, de Castro J, Migliorino MR, Helland A*, et al.* Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol. 2018;29(6):1409-16.
7. Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G*, et al.* Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017;18(7):874-86.
8. Ou SH, Janne PA, Bartlett CH, Tang Y, Kim DW, Otterson GA*, et al.* Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. Ann Oncol. 2014;25(2):415-22.
9. National Institute for Health and Care Excellence (NICE). Lung cancer: diagnosis and management: National Institute for Health and Care Excellence (NICE); 2019 28/03/19.
10. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C*, et al.* Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Annals of Oncology. 2018;30(5):iv192-iv237.
11. Zhou Z, Zhang J, Fan L, Zhang C, Xie J. Cost-effectiveness of ceritinib in the treatment of previously treated anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer in The United Kingdom. Value Health. 2015;18(7):A455-A6.
12. Scottish Intercollegiate Guidelines Network. SIGN 137: Management of lung cancer. 2014.

This assessment is based on data submitted by the applicant company up to and including 13 December 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.