Pfizer Limited
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12th May 2023

Dear Sam Roberts,

APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION FOR LORLATINIB FOR THE FIRST-LINE TREATMENT OF ANAPLASTIC LYMPHOMA KINASE (ALK)-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

EXECUTIVE SUMMARY

Pfizer Limited ("Pfizer") wishes to appeal the above Final Appraisal Document ("FAD"), in which lorlatinib is not recommended within its marketing authorisation for the first-line treatment of ALK-positive advanced NSCLC. Pfizer is disappointed by the Appraisal Committee's decision and disagree with the various judgements and assumptions the Committee made on key aspects of the evidence-base. Considering the evidence submitted during the appraisal process and the input of experts, the Committee has reached a conclusion based on the most conservative assumptions available. Pfizer therefore wishes to appeal this decision on the following grounds:

Ground 1

1.1 The committee has failed to explain how (if at all) it has taken into account the benefits of lorlatinib in preventing CNS progression in its decision making

Ground 2

2.1 The committee has been unreasonable in concluding that the original model structure could never be accepted, even with further data collection

2.2 The committee has been unreasonable in determining that future CROWN data is not generalisable to UK clinical practice on the basis of the currently available data

2.3 The committee has been unreasonable in not capturing the benefits of preventing CNS progression and concluding that this would not materially affect its decision, given the high impact on the ICER of excluding the CNS-PD health state

INTRODUCTION

Pfizer refers to its original submission in this appraisal. While a summary is provided below, this is not intended to replace the details originally supplied to NICE.

In the UK, 80–85% of lung cancers are classified as non-small cell lung cancer (NSCLC), with ALK gene translocations presenting in 3–7% of NSCLC tumours. Patients with NSCLC often have no or light smoking history and are typically diagnosed at a relatively young age compared with the overall lung cancer population. Due to the usually asymptomatic nature of lung cancer in the early stages, and the lack of smoking history, patients often have advanced disease at the time of diagnosis

Brain metastases are highly prevalent in patients with ALK-positive NSCLC. Brain metastases are associated with substantial mortality and morbidity, causing patients to experience confusion, drowsiness, weakness in the limbs and severe headaches.

First line treatment of patients with ALK-positive advanced NSCLC, who have not previously received an ALK inhibitor as recommended by NICE generally comprises crizotinib, alectinib or brigatinib. However, in view of the poor survival outcomes seen in patients with brain metastases, their low quality of life and the associated high economic burden, there remains a substantial unmet need for treatments that can penetrate the CNS more effectively than currently available therapies.

Lorlatinib is a third-generation ALK TKI which was specifically designed to penetrate the CNS through the introduction of a macrocyclic ring. In the CROWN clinical trial, lorlatinib was associated with lower 12-month cumulative incidence of CNS progression versus crizotinib in patients with (7% v 72%) and without (1% v 18%) brain metastases at baseline.

Lorlatinib has ORBIS designation as an innovative product and offers the potential for substantially improved outcomes over alectinib and brigatinib. This level of innovation is reflected in the fact that whilst there is currently substantial uncertainty within the PFS, IC-progression and OS estimates from CROWN, these are not primarily due to limited follow-up, but due to the performance of lorlatinib (limited events have occurred in the lorlatinib arm).

PROCEDURAL HISTORY OF THE APPRAISAL

Date	Event
March 2021	Referral to NICE
23 September 2021	The UK Licensing Authority granted marketing authorisation for lorlatinib in this indication (via ORBIS)
10 June 2021	Final scope for appraisal
12 May 2022	Pfizer submission to NICE
19 January 2023	First meeting of the Appraisal Committee
02 February 2023	Appraisal Consultation Document issued "Lorlatinib is not recommended, within its marketing authorisation, for treating ALK-positive advanced NSCLC in adults who have not had an ALK inhibitor."
02 March 2023	Pfizer and other consultees and commentators submit responses to consultation on ACD.
16 March 2023	Second meeting of the Appraisal Committee
19 April 2023	Final Appraisal Determination issued Recommendations unchanged from those in ACD
12 May 2023	Deadline for submission of appeal

GROUNDS OF APPEAL

1. GROUND 1: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS a) FAILED TO ACT FAIRLY OR b) EXCEEDED ITS POWERS

1.1. Appeal Point 1.1: The committee has failed to explain how (if at all) it has taken into account the benefits of lorlatinib in preventing CNS progression in its decision making

At paragraph 3.14 of the FAD, the committee acknowledged that:

> *"Removing the CNS PD health state also had its limitations, such as not capturing the potential benefit of lorlatinib in preventing CNS progression. It confirmed that it would take this into account in its decision making but, on balance, concluded removing the CNS PD health state was the most appropriate approach."*

However, despite recognising the importance of this benefit of lorlatinib treatment and stating in terms that it would be taken into account, the committee has provided no explanation of how prevention of CNS progression is reflected in its conclusions as set out in the FAD. It is therefore unclear whether this benefit has, in fact, been considered by the committee and, if so, how it has been weighed and assessed. Delay in CNS progression is a key benefit associated with lorlatinib therapy, which reflects its innovative nature and differentiates it from other therapies. However, the committee's reasoning and its approach to this benefit of treatment is wholly missing from the FAD. This lack of transparency is procedurally unfair.

Furthermore, the general approach of the committee, which was to adopt the most pessimistic assumption for each issue in the first appraisal committee meeting on 19th January 2023, which remained unchanged following the second appraisal committee meeting on 16th March 2023 as outlined in paragraph 3.24 of the FAD. The committee's preferred assumptions deviated from both the company and EAG's base-case's, with the committee instead opting for all the assumptions presented in an alternative pessimistic scenario presented by the EAG. Such an approach is inconsistent with any real weight being placed on the CNS benefits of lorlatinib, despite the committee's commitment at paragraph 3.14 of the FAD.

2. GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE

2.1. Appeal Point 2.1: The committee has been unreasonable in concluding that the original model structure could never be accepted, even with further data collection

A four health state (progression free, non-CNS progressed disease [PD], CNS PD and death) partitioned survival model, the 'original' model, was presented in the company evidence submission on 12 May 2022. This model structure was accepted for previous appraisals for previously untreated ALK-positive advanced NSCLC. At the March 2020 data cut from the pivotal study (CROWN) utilised within the 'original' model, most patients in both treatment arms were still alive, with only 23 (15%) patients in the lorlatinib arm and 28 (19%) of patients in the crizotinib arm having died. Given the immaturity of the data, several assumptions were required to model overall survival within a partitioned survival framework. These assumptions were transparently stated within Section B.3.3.2 of the manufacturer's original submission.

Paragraph 3.12 of the FAD states that:

> *"The EAG did not consider this model to be methodologically robust. This was because the model lacked transparency and the flexibility to explore alternative extrapolations of trial data."*

An alternative model, using post-progression survival (PPS) data sourced from other clinical trials was presented following the clarification meeting between the company, the EAG and NICE. As cited in paragraph 3.13 of the FAD, it was highlighted that this approach overcame inconsistencies when data was immature:

> *"The flexibility offered by a state-transition approach can also overcome inconsistencies in available survival evidence, which are more likely when that evidence is immature"*

Given that lorlatinib was under consideration for entry in the Cancer Drug Fund, the original model is still of relevance for an exit appraisal, when the evidence would be more mature (both in terms of events and duration). However, at paragraph 3.27 of the FAD, the committee concludes:

> *"It also noted the EAG's view that the original model structure did not represent a plausible alternative approach to modelling overall survival, even if further data was collected. So, it excluded any application of that model from its decision making."*

This conclusion by the Committee that the plausibility of the approach is unaffected by further data collection is unreasonable for the following reasons:

- Adopting a future view on the appropriateness of the original model structure in the absence of additional data from CROWN, cannot be considered reasonable, in circumstances where the original model structure was considered to be inappropriate due to immaturity of data.
- Relying on the EAG's view that the original model structure does not represent a plausible alternative to modelling overall survival with more mature data from CROWN without providing any additional justification.
- The committee have failed to explain why a partitioned survival modelling approach, which is standard in NICE oncology technology appraisals, would not be appropriate in a future submission. There is a reasonable likelihood that these concerns would not exist when further data is collected.

Furthermore, paragraph 3.12 of the FAD states that:

> *"The company accepted the EAG's concerns, and agreed at clarification stage to provide a revised model."*

This is a misinterpretation of the company's position at the clarification stage. It is factually inaccurate to conclude that the company accepted the EAG's concerns. As stated in the company clarification question response, a revised model was submitted 'to address the EAG's concerns' regarding the original model structure but does not indicate acceptance of all of the EAG's concerns regarding the model for any future re-submission with more mature survival data from the pivotal study.

2.2. Appeal Point 2.2: The committee has been unreasonable in determining that future CROWN data is not generalisable to UK clinical practice on the basis of the currently available data

In paragraph 3.27 of the FAD, the committee states:

> *"They also noted that, although more mature overall survival data will become available from CROWN, it will not be generalisable to NHS practice. This is because the subsequent treatments used in CROWN do not align with those used in the NHS. This means that overall survival in CROWN could be confounded or driven by subsequent use of second-generation ALK TKIs."*

This is contradictory to clinical advice received by the committee in the first committee meeting on 19th January 2023, as reported in paragraph 3.5 of the FAD:

> *"The clinical experts confirmed that subsequent treatments in clinical trials often have a confounding effect on overall survival results. They explained that, for the lorlatinib arm, there was no evidence that using second-generation ALK TKIs after third-generation lorlatinib would have any meaningful effect on overall survival, but that this is uncertain."*

Furthermore, it is unknown what subsequent treatments patients may have received at the next planned data cut. As of the September 2021 CROWN data cut, 91 of 149 patients (61.1%) vs 12 of 147 patients (8.2%) were still receiving lorlatinib vs crizotinib, respectively. In the lorlatinib arm, 33 of 149 patients (22.1%) received ≥1 subsequent systemic anticancer therapy, of whom 63.6% received an ALK TKI as first subsequent treatment, which represents only 14% of the 149 patients randomised into the lorlatinib arm of CROWN. In addition, at CDF exit, various established statistical methods could be employed to reduce any confounding caused by subsequent systemic anticancer therapy and real-world evidence maybe available to inform the magnitude of any confounding.

In addition, survival data across oncology trials often includes confounding subsequent treatment but the data has not been dismissed by NICE committee on previous occasions. For example, in TA654 (avelumab in renal cell carcinoma) despite the fact 'that many subsequent treatments used in the trial are not routinely used in the NHS' the overall survival data was accepted within the base-case ICER used for decision-making In previous appraisals for previously untreated ALK-positive advanced NSCLC, both alectinib and brigatinib were recommended by the committee despite uncertainty around subsequent treatments and their effect on OS (TA536 and TA670).

The committee have taken an unreasonable position on the applicability of future survival data from CROWN considering the clinical advice received and the unknown number of patients who will have

progressed onto a subsequent treatment in future data cuts and in circumstances where such data are not known and have not been considered by the committee.

2.3. <u>Appeal Point 2.3: The committee has been unreasonable in not capturing the benefits of preventing CNS progression and concluding that this would not materially affect its decision, given the high impact on the ICER of excluding the CNS-PD health state</u>

At paragraph 3.28 of the FAD:

> *"The committee concluded that its preferred model structure could mean that there were CNS benefits associated with lorlatinib that had not been fully captured"* but stated *"Overall, it concluded that allowing for lorlatinib's potential uncaptured benefits would not materially affect its decision"*

The impact on the ICER of removing the CNS-PD health state health was classified as high within slide 9 in the first appraisal committee meeting. This committee conclusion that the exclusion of the CNS-PD health state has no material impact, contradicts the available evidence and is therefore unreasonable.

<u>THE DETERMINATION OF THIS APPEAL</u>

Pfizer requests that this appeal should be determined at an oral hearing.

<u>REQUESTED OUTCOME FOLLOWING APPEAL</u>

<u>Pfizer respectfully requests the Appeal Panel to return this appraisal to the Appraisal Committee for further consideration with the following directions:</u>

- That it should provide clarification as to how the uncaptured CNS benefit of lorlatinib was accounted for in its decision making
- To recognise that the original partitioned survival model structure submitted by the company may be appropriate when further OS data from the pivotal trial are available and could therefore be considered when assessing future plausible cost-effectiveness
- That its conclusions regarding the generalisability of future CROWN data to UK clinical practice are not reasonable
- That it should reconsider its position that lorlatinib's potential uncaptured benefits would not materially affect the committee's outcome.