7.11 CRIZOTINIB, 200 mg capsule, 60 and 250 mg capsule, 60, Xalkori®, Pfizer Australia Pty Ltd.

1 Purpose of Application

1.1 A resubmission to request Authority Required listing for treatment of a patient with anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC) who meets certain criteria.

2 Requested listing

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer
CRIZOTINIB			
crizotinib 200 mg capsule	60	1	Xalkori Pfizer
crizotinib 250 mg capsule	60	1	

Severity:	Locally advanced or metastatic
Condition:	non-small cell lung cancer
Treatment phase:	Initial treatment
Restriction:	Authority Required
Clinical criteria:	Patient must have a WHO performance status of 2 or less. AND Patient must have disease progression following treatment with a least 1 platinum-based chemotherapy agent. AND Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material. AND The treatment must be as monotherapy.

2.1 The requested basis for listing is cost-effectiveness compared with pemetrexed.

2.2 The PBAC previously proposed that any PBS-subsidised use of crizotinib should consider the following (a) tumour histology - possibly limiting use to adenocarcinoma; (b) presence of coexistent mutations which confer resistance to crizotinib; and (c) extent of pre-treatment with other agents. The sponsor indicated its willingness to work with the Department on the appropriate wording of a PBS restriction. The PBAC also previously proposed to cease any PBS subsidy of crizotinib following disease progression. The pre-PBAC response referred to additional clinical evidence to support the sponsor's request to allow crizotinib to be continued beyond disease progression (see below). The PBAC considered that crizotinib is likely to be used after disease progression, even if the PBS restriction included a note to advise that crizotinib should not be continued if there is no clinical benefit, and so advised that this use should be reflected in the financial estimates.

3 Background

3.1 Crizotinib was TGA-registered on 27 September 2013 for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). The PBAC has considered crizotinib once previously.

3.2 The November 2013 PBAC meeting deferred its consideration of crizotinib. The sponsor lodged a minor resubmission offering an initial confidential special pricing arrangement to reduce the dispensed price of crizotinib by [redacted]% from $[redacted] to an effective price of $[redacted] and requesting PBAC consideration of a proposed managed entry scheme (MES) through which a maximum [redacted]% price reduction is offered to match the price of pemetrexed. The pre-PBAC response to the Department's overview of the submission withdrew the proposal for an MES, agreeing that it would not be of benefit to the government or the applicant.

3.3 The PBAC previously sought the following advice of the Medical Services Advisory Committee (MSAC) advice on co-dependent testing of ALK gene rearrangements:

a) whether ALK gene rearrangement testing should be restricted to particular NSCLC subtypes;
b) whether patients with evidence of likely crizotinib-resistant mutations should be excluded from ALK gene rearrangement testing;
c) whether testing should be extended to include other rare targets for crizotinib;
d) what should be the place of testing for ALK expression;
e) whether the timing of testing of patients with NSCLC should be restricted;
f) whether there are any aspects of an MBS item descriptor which would facilitate practical implementation in pathology practice; and
g) whether ALK gene rearrangements are a positive prognostic factor.

3.4 The resubmission: (a) supported limiting ALK testing to patients with non-squamous or 'not otherwise specified' NSCLC; (b) stated that no data are yet available to identify likely crizotinib resistant mutations; (c) stated that no data are yet available to identify other crizotinib sensitive mutations; (d) committed the sponsor to work with the Department to cross-reference to ALK immunohistochemistry (IHC); (e) proposed limiting ALK testing to only those with advanced or metastatic NSCLC; (f) stated that the sponsor is actively engaged with the pathology community, seeking consensus for implementation; and (g) concluded that "ALK-positive patients experience similar survival to ALK-negative patients" based on its literature review of 27 retrospective and. The submission repeated its conclusion that ALK-positivity is not a favourable prognostic factor.

3.5 The PBAC noted that in November 2013 the MSAC deferred its consideration of providing advice to the Minister and the PBAC in the related matter of ALK testing. MSAC sought further information from the applicants, Roche Diagnostics (particularly in relation to more expensive antibody clones and more complex than usual IHC testing) and the Royal College of Pathologists of Australasia (particularly in relation to optimising ALK testing). The PBAC further noted that Abbott Molecular (the co-applicant for the co-dependent ALK testing technology) was expected to lodge a separate submission to MSAC to address all of the issues raised by MSAC. PBAC also noted that the Royal College of Pathologists of Australasia were preparing a response to MSAC. The PBAC agreed that MSAC advice was particularly important in the context of crizotinib given the complexity of testing and the low prevalence of ALK gene rearrangements.

3.6 The PBAC considered that the quality and oversight of ALK testing are fundamental prerequisites for the use of crizotinib, noting that patients will be poorly advised,

disadvantaged and potentially harmed if optimal testing (including the appropriate oversights) are not put in place.

4 Clinical place for the proposed therapy

4.1 Crizotinib was proposed for PBS listing as second-line therapy (following disease progression after treatment with a least one platinum-based chemotherapy agent) in ALK-positive patients with locally advanced or metastatic NSCLC.

5 Comparator

5.1 The resubmission accepted the November 2013 PBAC preference for pemetrexed as the sole comparator rather than a mix of pemetrexed and docetaxel.

6 PBAC consideration of the evidence

Consumer comments

6.1 The PBAC noted the comment received from the Medical Oncology Group of Australia (MOGA). MOGA noted the response rate for crizotinib of 57%. Phase I/II and recently Phase III randomised trials have demonstrated a significant improvement in PFS in the second line metastatic sitting with crizotinib compared with standard chemotherapy. MOGA also noted that only 5% of NSCLC may benefit from treatment with crizotinib, the safety profile is not yet clearly established and the emergence of resistance to crizotinib.

Clinical trials

6.2 The clinical trial forming the basis of the comparison between crizotinib and pemetrexed was unchanged from the previous submission. Additional clinical studies were presented for crizotinib:

- The Lung Cancer Genome Project 2013: a non-randomised comparison of crizotinib treated and crizotinib-naïve in 30 patients with ALK-positive lung cancer using a nested cohort study design;
- Zhang 2014: a non-randomised comparison of crizotinib treated and crizotinib-naïve in 51 patients with ALK-positive lung cancer using a study design which is not clear in relation to the ascertainment of ALK status; and
- Berge 2013: a retrospective study comparing crizotinib followed by pemetrexed with pemetrexed followed by crizotinib in 38 patients with ALK-positive NSCLC).

For pemetrexed, the submission presented a literature review to ascertain the OS gain with second-line pemetrexed monotherapy in patients with stage IIIB/IV NSCLC to form a basis to indicate that overall survival results with pemetrexed have not changed in the 10 years since the Hanna (2004) publication).

6.3 However, the PBAC noted that the all eligible studies in this literature review of pemetrexed included patients who were not selected as being ALK-positive. Given that some 94% of the patients in this review would be ALK-negative, the PBAC considered that this review was not relevant because being ALK-positive appears to predict an improved treatment effect for pemetrexed as well as crizotinib.

6.4 The pre-PBAC response also referred to Ou, 2014: a non-randomised retrospective analysis of the Phase I and II studies of crizotinib (A8081001 and A8081005) comparing patients who continued crizotinib beyond progressive disease and those

who did not to support its request to allow PBS-subsidised crizotinib to be continued beyond disease progression. The PBAC agreed with the authors and the pre-PBAC response that those who continued crizotinib could simply represent a subgroup with favourable prognostic factors, rather than a direct post-progressive disease treatment effect.

Comparative effectiveness

6.5 As previously, the PBAC considered that crizotinib is more effective than pemetrexed with a difference in median progression-free survival gain of 3.5 months. However, the estimate of incremental overall survival gain (12.0 months) was less convincingly demonstrated. The PBAC noted the additional studies (one set for crizotinib and one set for pemetrexed) presented in the resubmission were not directly comparative. The PBAC considered that they were insufficient to support the assumption across both submissions of a ratio of incremental median gain between progression-free survival and overall survival should consistently approximate one to three (i.e., that for every one month increase in progression-free survival there should be a corresponding increase in overall survival of approximately three months). The additional information did not change the November 2013 PBAC conclusion that this assumption was implausible.

6.6 As previously, the PBAC considered that its main concern with the applicability of the evidence for pemetrexed relied upon by the applicant is that it is mostly in patients with ALK-negative NSCLC. Pemetrexed is the current standard of care for patients with adenocarcinomas and is more effective than other current chemotherapies in patients with ALK-positive NSCLC (Camidge, DR et al J Thoracic Oncol 2011;6(4):774-80; Lee, JO et al J Thoracic Oncol 2011;6(9):1474-80; and Berge EM, et al Clin Lung Cancer 2013;14(6):636-43). These studies indicate that pemetrexed has an improved treatment effect in patients with ALK-positive NSCLC compared to patients with ALK-negative NSCLC.

Comparative harms

6.7 The PBAC did not change its previous conclusions in relation to comparative harms, remaining concerned by the high incidence of visual disturbances, male hyopogonadism and gastrointestinal disturbance and considering that visual disturbances warranted further investigation in particular.

Clinical claim

6.8 As previously, the PBAC accepted the claims for crizotinib having superior effectiveness and non-inferior safety compared to pemetrexed, but considered that the approach taken in the original submission and repeated in the resubmission overestimated the incremental overall survival gain.

Economic analysis

6.9 The PBAC previously requested that any resubmission provide results of the economic evaluation for a respecified base case which: (a) reduced the incremental overall survival gain to 3.1 or 3.5 months; (b) included costs for broader mutation testing; (c) included costs to manage adverse events; and (d) reduced the crizotinib price to achieve an ICER in the order of $50,000-$60,000 per QALY.

6.10 The economic evaluation in the resubmission: (a) retained the incremental median OS per treated patient as 12.0 months; (b) did not include broader mutation testing costs; (c) included a nominal annual cost of [redacted] for ophthalmological testing costs included; and (d) reduced crizotinib price to estimate a revised ICER of between $45,000 to $75,000/QALY (reduced from the previous ICER of between $45,000 and $75,000/QALY).

6.11 The pre-PBAC response reported that, if the model is revised to reduce the overall survival of crizotinib towards that of pemetrexed, the ICER is between $75,000 and $105,000/QALY for a 3.1 incremental overall survival gain and between $75,000 and $105,000/QALY for a 3.5 incremental overall survival gain, and if the model is revised to increase the overall survival of pemetrexed towards that of crizotinib, the ICER is between $105,000 and $200,000/QALY for a 3.1 incremental overall survival gain and between $105,000 and $200,000/QALY for a 3.5 incremental overall survival gain.

6.12 The PBAC noted from the analyses varying the overall survival of crizotinib, that at least a 30% price reduction would be needed to achieve an acceptable ICER. Adjusting for an improved overall survival in patients with ALK-positive NSCLC treated with pemetrexed would necessitate a further price reduction.

Estimated PBS usage & financial implications

6.13 The resubmission revised its previous estimated PBS usage and financial implications to less than $10 million per year, reflecting pemetrexed alone as the comparator, the PBAC proposal to not allow PBS-subsidised use of crizotinib after disease progression, and the proposed reduced price of crizotinib. The PBAC considered that, if PBS-subsidised use of crizotinib after disease progression were to be accepted, then this should be reflected in the financial estimates, increasing the estimates but still less than $10 million per year.

7 PBAC Outcome

7.1 The PBAC again deferred its consideration of crizotinib to ascertain the applicant's input on the Committee's proposed approach to achieve acceptable cost-effectiveness and until such time as MSAC decides to support the corresponding MBS listing of ALK in-situ hydridisation (ISH) testing (and any other associated molecular testing advised by MSAC) for patients with NSCLC.

7.2 The PBAC reaffirmed its intention that any PBS-subsidised use of crizotinib should be consistent with proposed MBS descriptors for ALK testing and the definition of ALK positive tumours. PBAC considered that crizotinib is likely to be used after disease progression, even if the PBS included a note to advise that crizotinib should not be continued if there is no clinical benefit, and so foreshadowed that it would be unlikely to recommend a stopping rule, which should be reflected in the financial estimates.

7.3 The PBAC noted that the November 2013 MSAC deferred its consideration of ALK testing, seeking further information from the applicants, Roche Diagnostics and the Royal College of Pathologists of Australasia. The PBAC agreed that MSAC advice was particularly important in the context of crizotinib given the complexity of testing and the low prevalence of ALK gene rearrangements. The PBAC considered that the quality and oversight of ALK testing are fundamental prerequisites for the use of crizotinib, noting that patients will be poorly advised, disadvantaged and potentially harmed if optimal testing and oversight of laboratory test standards is not put in place.

7.4 The PBAC reaffirmed its previous conclusion that the claim of incremental overall survival gain of 12.0 months for crizotinib over pemetrexed was implausible. As previously, the PBAC considered that its main concern with the applicability of the evidence for pemetrexed relied upon by the applicant is that it is mostly in patients with ALK-negative NSCLC. Studies of pemetrexed in patients with ALK-positive NSCLC indicate that pemetrexed has an improved treatment effect in patients with ALK-positive NSCLC than in patients with ALK-negative NSCLC.

7.5 The PBAC noted that the resubmission's economic evaluation only adopted its requested respecified base case in the following respects: (a) used the costs of pemetrexed only as the comparator; (b) included a nominal [redacted]/year for the costs of managing the adverse events of crizotinib, and (c) reduced the crizotinib price. The PBAC noted that the following requests were not adopted: (a) reduce the incremental overall survival gain to 3.1 or 3.5 months (the estimate of 12.0 months was retained); (b) include costs for broader mutation testing (which extend beyond the cost per patient tested of ALK ISH testing); and (c) reduce the crizotinib price to achieve an ICER in the order of between $45,000 to $75,000 per QALY (the ICER presented was between $45,000 and $75,000). The PBAC further noted that the model was sensitive to how it is adjusted to reflect an incremental overall survival gain which the Committee considered to be more strongly supported by the available evidence. The PBAC concluded that, from the analyses varying the overall survival of crizotinib presented in the per-PBAC response, at least a 30% price reduction would be needed to achieve an acceptable ICER, and a greater price reduction should be required because the less confidently estimated overall survival of pemetrexed should be increased consistent with the evidence of an improved treatment effect in patients with ALK-positive NSCLC.

7.6 The PBAC noted that, in the event of a positive recommendation to list crizotinib, the matters for implementing such a recommendation identified in its November 2013 consideration would still apply.

7.7 The PBAC considered that any further submission for crizotinib should be a major submission incorporating the advice from MSAC, subject to independent evaluation and consideration by the Economics Sub-Committee.

7.8 The PBAC noted the generally supportive comments from the Medical Oncology Group of Australia describing crizotinib as the new second-line standard of care in patients with ALK-positive NSCLC, but also advising that post-marketing data would help ascertain both the safety profile of crizotinib and the consequences of the emergence of resistance on the effectiveness of crizotinib.

Outcome:
Deferred

Context for Decision
The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Taking into account the totality of the evidence, the Sponsor considers that the base-case $/QALY for crizotinib is within the requested range - which is at the lower end of the range that Oncology medicines have previously received positive recommendations.

In light of the targeted mode of action of crizotinib, defined patient population, supported by the unprecedented survival (median PFS of 7.7 months and median OS of 20.3 months) following disease progression with at least one platinum-based chemotherapy, the statistically significant improvements in quality of life, manageable side-effect profile and the low budget impact the Sponsor urges the Committee to allow Australian patients timely access to crizotinib, a new, targeted clinical advance for a previously untreatable patient population.