

7.13 CRIZOTINIB, 250 mg capsule, 200 mg capsule, Xalkori[®], Pfizer Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor resubmission requested a new Section 85 Authority Required PBS listing for crizotinib for the treatment of patients with locally advanced (Stage IIIB) or metastatic (Stage IV) c-ROS proto-oncogene 1 (ROS1) positive non-small cell lung cancer (NSCLC).
- 1.2 Following consideration, and deferral, by the PBAC at the November 2017 meeting, this minor resubmission sought to:
 - propose an alternate restriction, allowing treatment agnostic of line of therapy;
 - address the uncertainty surrounding the magnitude of the clinical benefit and respecify the base case incremental cost-effectiveness ratio (ICER); and
 - develop an appropriate pricing strategy.

2 Requested listing

- 2.1 The restriction requested in the November 2017 submission was for second-line therapy following platinum-based chemotherapy.
- 2.2 In the November 2017 Public Summary Document (PSD), the PBAC “foreshadowed its intention to remove the criterion ‘The condition must have progressed on or after prior platinum based chemotherapy’ from any recommended initial and grandfathering treatment criteria to allow the PBS listing of crizotinib in the ROS1-positive NSCLC population to be agnostic of line of therapy, consistent with its current listing in the anaplastic lymphoma kinase (ALK)-positive NSCLC population. The PBAC advised that all other aspects of the restriction requested, with proposed changes by the Secretariat, would be appropriate.” (paragraph 7.3, November 2017 PSD)
- 2.3 The minor resubmission therefore requested the following restriction, which is agnostic to line of treatment:

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed price for maximum quantity	Proprietary Name and Manufacturer
CRIZOTINIB Capsule, 200 mg, 60	1	1	\$7,277.82 (Published) \$ [REDACTED] (Effective) \$ [REDACTED] (Weighted effective)	Xalkori® Pfizer
CRIZOTINIB Capsule, 250 mg, 60	1	1	\$7,277.82 (Published) \$ [REDACTED] (Effective) \$ [REDACTED] (Weighted effective)	Xalkori® Pfizer

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	Non-small cell lung cancer
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have a WHO performance status of 2 or less.
Population criteria:	Patient must have evidence of ROS1 gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.
Prescriber instructions:	The authority application must be made in writing and must include: (1) A completed authority prescription form; and (2) A completed ROS1-Positive Non-Small-Cell Lung Cancer Authority Application – Supporting Information Form, which includes details of ROS1 gene rearrangement in tumour material.
Administrative advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	Non-small cell lung cancer
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.</p>
Prescriber instructions:	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Administrative advice:	<p>No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	Non-small cell lung cancer
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer
Treatment phase:	Grandfathering treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [PBS listing date], AND The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patients may qualify for PBS-subsidised treatment under this restriction once only.</p>
Population criteria:	Patient must have evidence of ROS1 gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.
Prescriber instructions:	<p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) A completed authority prescription form; and (2) A completed ROS1-Positive Non-Small-Cell Lung Cancer Authority Application – Supporting Information Form, which includes details of ROS1 gene rearrangement in tumour material.
Administrative advice:	<p>No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

2.4 The proposed restriction was for an Authority Required (In Writing) listing for initial treatment and an Authority Required (Telephone) listing for continuing treatment and grandfathered patients. The minor resubmission suggested an Authority Required (Telephone) listing for initial treatment to reduce the administrative burden and minimise delay in initiating patients could be considered.

3 Background

3.1 Crizotinib is TGA registered for:

“the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC), AND the treatment of patients with ROS1-positive advanced non-small cell lung cancer (NSCLC).”

- 3.2 Crizotinib for advanced ROS1-positive NSCLC was considered as a co-dependent integrated submission (with ROS1 fluorescent in-situ hybridisation (FISH) testing) at the November 2017 PBAC meeting. The PBAC deferred its decision. The MSAC foreshadowed its support for a new MBS item for ROS1 FISH testing to inform eligibility for crizotinib treatment in this population (Public Summary Document, Application No. 1454, crizotinib, November 2017 MSAC meeting).
- 3.3 The November 2017 submission was the result of an invitation from the PBAC to the Sponsor for a submission for this rare cancer. Crizotinib for ALK-positive Stage IIIB or Stage IV non-squamous or histology not otherwise specified (NOS) NSCLC was listed on the PBS on 1 July 2015.

For more detail on PBAC's view, see Section 6 PBAC outcome.

4 Comparator

- 4.1 The previous major submission considered by the PBAC in November 2017 nominated pemetrexed as the comparator. This was reasonable, and was appropriately unchanged in the minor resubmission.

5 Consideration of evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from individuals (6) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with crizotinib, and emphasized the effectiveness of targeted therapies like crizotinib in reducing tumour burden and improving quality of life.
- 5.3 A comment from Lung foundation Australia noted that the PBS listing of crizotinib would make a meaningful difference in the lives of the small population of ROS1-positive NSCLC patients.
- 5.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the crizotinib submission, noting that the PBS listing of crizotinib in this population would fill a significant area of unmet need. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for crizotinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on single arm studies.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Economic analysis

5.5 In the previous major submission considered by PBAC in November 2017, the submission presented a cost-effectiveness analysis against pemetrexed. The minor re-submission did not alter the economic model structure from November 2017 but sought to respecify the best estimate of the base case ICER by addressing the PBAC's concerns surrounding:

- the efficacy of the comparator, pemetrexed;
- the incremental effectiveness of crizotinib versus pemetrexed; and
- pemetrexed cost offsets.

The respecified base case ICER was verified by the Department.

Pemetrexed efficacy

5.6 The PBAC had considered (paragraph 7.8, November 2017 PSD) “that the effectiveness of pemetrexed was potentially underestimated as (i) study patients received fewer cycles of treatment than Australian practice (as estimated by Australian clinicians); (ii) its supporting study included patients with squamous NSCLC who have worse outcomes with pemetrexed, and (iii) other treatment practices may have improved since the study was conducted (2001 to 2003).”

5.7 In the pre-PBAC response to the November 2017 meeting, a further sensitivity analysis was performed in which the overall survival outcomes for patients treated with pemetrexed were increased by a factor of [REDACTED]. This increased the median overall survival in the comparator arm to 10 months, which was more consistent with the more contemporary survival response seen in the chemotherapy (docetaxel) arm of the Phase III study of nivolumab in advanced non-squamous NSCLC, which informed the positive PBAC recommendation for nivolumab in March 2017 (Nivolumab PSD, March 2017).

5.8 The factor of [REDACTED] was applied to the pemetrexed arm of the revised base case presented in the minor resubmission.

Incremental effectiveness

5.9 The PBAC had noted (paragraph 7.9, November 2017 PSD) “although crizotinib was likely to be more effective than pemetrexed, the magnitude of the incremental effectiveness was difficult to estimate” and “the incremental effectiveness of crizotinib over pemetrexed was overestimated in the submission; however....the Committee was satisfied that the incremental effectiveness of crizotinib treatment in the ROS1-positive NSCLC population would be similar to that in the ALK-positive NSCLC population.”

5.10 The PBAC had recalled that (paragraph 7.12, November 2017 PSD) “it had recommended crizotinib in the ALK population based on evidence from a direct randomised controlled trial (A8081007/Ou, 2012) ...and in the absence of similar

robust evidence to determine the incremental benefit and therefore the cost-effectiveness of crizotinib in the ROS1-positive NSCLC setting, and assuming a similar effectiveness across these two biomarker-defined populations, the cost of treating a ROS1-positive patient should be the same as treating an ALK-positive patient. The PBAC considered that this conclusion of similarity was generous from the perspective of biological plausibility, because (i) although the ROS1 and ALK genes are evolutionarily related, the kinase domains of ROS1 and ALK show only about 49% amino acid sequence homology²; and (ii) ALK inhibitors have lower affinity (IC₅₀) for ALK than ROS1 in vitro indicating that ALK inhibitors are better at inhibiting ALK expression than at inhibiting ROS1 expression. PBAC acknowledged that this data is not based on observations of clinically meaningful outcomes.”

5.11 The minor resubmission did not agree with a conclusion of equivalent incremental benefit across patient populations with different driver mutations informed by in vitro evidence alone. The minor resubmission stated that Ou, 2012 references in vitro evidence of the inhibition of ROS1 by four different ALK inhibitors and concludes that “Despite sharing only approximately 49% amino acid sequence homology in the kinase domains between ALK and ROS1, there is now growing evidence that at least several ALK inhibitors are also potent ROS1 inhibitors in vitro.” The minor resubmission stated that:

- The evidence of lower affinity (IC₅₀) against ALK versus ROS1 was based on in vitro studies of the ALK inhibitors brigatinib and WZ-5-126, not from crizotinib specifically; and
- Each of the ALK inhibitors has a different pharmacodynamic profile.

5.12 The minor resubmission stated that the efficacy outcomes derived from the pivotal crizotinib studies presented previously (A8081001 and OO12-01) provided the highest level of available evidence (combined analysis, ██████ PFS = █████ months; 95% CI: █████, █████; median OS = █████; 95% CI: █████, █████).

5.13 In order to address some of the uncertainty surrounding the magnitude of benefit, the minor resubmission proposed applying a more conservative modelled survival outcome, by reducing the time horizon in the base case from 10 years to 5 years.

5.14 The pre-PBAC response claimed that a time horizon of 5 years would be conservative, and noted that this was consistent with the time horizon in the economic evaluation which informed PBAC decision-making for nivolumab for the treatment of advanced non-squamous NSCLC (nivolumab PSD, March 2016).

Pemetrexed cost offsets

5.15 The cost of pemetrexed was updated to reflect the current PBS prices (1 April 2018). In the model, the cost of treatment for 21 days was reduced from \$540.79 to \$228.64.

² Expert Rev Anticancer Ther. 2012 Apr;12(4):447-56. doi: 10.1586/era.12.17

Results of the revised economic evaluation

- 5.16 The updated economic evaluation, which included the three changes described above, and the updated DPMQ for crizotinib of \$ [REDACTED], resulted in an ICER of \$45,000/QALY - \$75,000/QALY (as compared to \$45,000/QALY - \$75,000/QALY in the previous submission).
- 5.17 The table below compares the ICERs obtained if the updated DPMQ and original DPMQ (as proposed in the November 2017 submission) for crizotinib were used in the updated model.

Table 1: Updated ICERs for the proposed ROS1 listing of crizotinib

		ICER based on Nov 2017 [REDACTED] (\$ [REDACTED])	ICER based on Jul 2018 DPMQ (\$ [REDACTED])
	Base case November 2017	\$ [REDACTED]	-
1	November 2017 submission with updated pemetrexed pricing (as per PBS, April 2018)	\$ [REDACTED]	\$ [REDACTED]
2	Updated pemetrexed pricing AND increased pemetrexed efficacy (10 months median overall survival)	\$ [REDACTED]	\$ [REDACTED]
3	Updated pemetrexed pricing AND time horizon reduced from 10 years to 5 years	\$ [REDACTED]	\$ [REDACTED]
4	New base case (1, 2 and 3 applied)	\$ [REDACTED]	\$ [REDACTED]

Source: Table 1, p8 of the minor resubmission

DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; ROS1 = c-ROS proto-oncogene 1

Drug cost/patient/course: \$ [REDACTED].

- 5.18 The drug cost per patient per course of \$ [REDACTED] was based on the proposed DPMQ of \$ [REDACTED] for 30 days treatment and a median progression free survival of [REDACTED] months. Using the same calculations and the DPMQ proposed in November 2017 (\$ [REDACTED]), the drug cost per patient per course was \$ [REDACTED].

Estimated PBS usage & financial implications

- 5.19 The PBAC had advised (paragraph 7.15, November 2017 PSD) “the utilisation assumptions supporting the financial estimates were reasonable from a PBS perspective after adjusting the estimate of eligible patients in the first year to include patients who would receive treatment under the proposed grandfathering arrangement.”
- 5.20 The minor resubmission indicated that as of 14 March 2018, there were [REDACTED] NSCLC patients with confirmed ROS1 rearrangements receiving compassionate supply of crizotinib. This was assumed to be the number of patients who would be initiated on treatment through the proposed grandfathering arrangement.

5.21 The utilisation estimates were also updated to reflect a PBS restriction that is agnostic to line of therapy. The minor resubmission assumed that █% of ROS1 positive NSCLC patients would receive treatment with crizotinib via the PBS, as compared to █% in the November 2017 submission receiving second-line therapy.

5.22 The minor resubmission also updated the financial estimates to incorporate the following changes:

- Updated crizotinib prices to reflect new effective DPMQ and updated pemetrexed prices to 1 April 2018 PBS prices;
- PBS data for crizotinib used to estimate the split of dispensing by beneficiary category and patient co-payments were updated to the 2017 calendar year;
- PBS data for pemetrexed used to estimate the PBS volumes displaced were updated to the 2017 calendar year; and
- The dispensing fees and co-payments were updated to 2017 prices.

5.23 The updated financial estimates are presented in the table below.

Table 2: Updated financial estimates for the treatment of ROS1-positive NSCLC with crizotinib (using the effective █ of \$█)

	Year 1: 2018	Year 2: 2019	Year 3: 2020	Year 4: 2021	Year 5: 2022	Year 6: 2023
Number of ROS1-positive patients initiated onto crizotinib	█	█	█	█	█	█
Cost to the PBS/RPBS of crizotinib treatment	\$█	\$█	\$█	\$█	\$█	\$█
Cost to the PBS/RPBS of pemetrexed displaced	\$█	\$█	\$█	\$█	\$█	\$█
Total net cost to the PBS/RPBS of the listing	\$█	\$█	\$█	\$█	\$█	\$█
Total cost of proposed ROS1 testing algorithm to the MBS	\$█	\$█	\$█	\$█	\$█	\$█
Total net cost to Government Health Budget	\$█	\$█	\$█	\$█	\$█	\$█

Source: Table 2, p9 of the minor resubmission

FISH = fluorescent in-situ hybridisation; IHC = immunohistochemistry; MBS = Medicare Benefits Schedule; NSCLC = non-small cell lung cancer; PBS = Pharmaceutical Benefits Schedule; RPBS = Repatriation Pharmaceutical Benefits Scheme; ROS1 = c-ROS proto-oncogene 1

5.24 The estimated cost to the PBS/RPBS for the proposed agnostic line listing for the treatment of ROS1-positive NSCLC was less than \$10 million in Year 1, increasing to less than \$10 million in Year 6. The cost over the first six years of listing to the PBS/RPBS was estimated to be \$20 - \$30 million. The Department verified the financial estimates presented in the minor resubmission.

Weighted average price

5.25 In November 2017 the PBAC had advised (paragraph 7.13, November 2017 PSD) “that the cost per patient of crizotinib in the ROS1-positive setting should be the same as that in the ALK-positive setting, that is, after adjusting the effective DPMQ in

the ROS1-positive setting to account for the difference in observed treatment durations in each setting (██████████ and 7.7 months respectively). A weighted average effective DPMQ could then be calculated across the two settings.”

- 5.26 The minor resubmission agreed with the request for a single weighted average effective DPMQ across the two reimbursed populations of NSCLC patients and noted that this would simplify the Special Pricing Arrangements and associated contractual requirements.
- 5.27 The proposed weighted average price in the resubmission across the two settings was derived from:
- The estimated average annual gross PBS/RPBS expenditure for the proposed ROS1 listing over the first 5 years of listing, as described above; and
 - The actual PBS expenditure for crizotinib for the treatment of ALK-positive NSCLC over the 12 months, February 2017 to January 2018.
- 5.28 It was calculated that the proportion of expenditure across the ALK and ROS1 indications ██████████ be ██████████% and ██████████% respectively. The resubmission used a ██████████% versus ██████████% split, as outlined in the table below.

Table 3: Weighted effective price calculations

Indication	Expenditure (before rebates)	Calculated % of total expenditure	Proposed % of total expenditure	Effective EMP	Weighted effective EMP price calculation
ALK	\$██████████	██████████%	██████████%	\$██████████	\$██████████ ^a
ROS1	\$██████████	██████████%	██████████%	\$██████████	\$██████████
Total					AEMP: \$██████████ DPMQ: \$██████████

^a This figure was incorrect in the table provided in the minor resubmission. The correct figure from the accompanying spreadsheet has been verified and presented here instead.

Source: Table 3, p11 of the minor resubmission

ALK = anaplastic lymphoma kinase; DPMQ = dispensed price for maximum quantity; EMP = ex-manufacturer price; ROS1 = c-ROS proto-oncogene 1

- 5.29 The weighted average effective AEMP and DPMQ of \$██████████ and \$██████████, respectively across the two settings represented a ██████████% price reduction compared with the current published AEMP for crizotinib in the ALK-positive setting.

For more detail on PBAC’s view, see Section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC recommended the listing of crizotinib for the treatment of ROS1-positive locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC). In making this recommendation, the PBAC acknowledged that there is a high unmet clinical need in the small proposed population (approximately ██████████ patients per year, 1.6% of all patients with NSCLC), and recalled that this submission was the result of an invitation from the PBAC to the sponsor for a submission for this rare cancer population. Further, the PBAC advised that crizotinib’s effectiveness and

safety profile in the ROS1-positive NSCLC population is likely to be similar to that in the ALK-positive NSCLC population, for which it is already PBS listed.

- 6.2 The PBAC noted that the MSAC had foreshadowed its support for a new MBS item for ROS1 FISH testing to inform eligibility for crizotinib treatment in this population (Public Summary Document, Application No. 1454, crizotinib, November 2017 MSAC meeting).
- 6.3 The PBAC recalled that it had foreshadowed its intention to recommend a listing agnostic to line of therapy (paragraph 7.3, November 2017 PBAC PSD). The PBAC therefore advised that the restriction requested by the sponsor in the resubmission, with proposed changes by the Secretariat, was appropriate.
- 6.4 The PBAC noted that the minor resubmission proposed a grandfather restriction for patients accessing crizotinib through the sponsor's compassionate access program, as well as those using crizotinib on a private prescription, for ROS1-positive NSCLC. The PBAC considered that the proposed grandfathering restriction was appropriate.
- 6.5 The PBAC noted that the minor submission did not present any additional clinical evidence on the safety and effectiveness of crizotinib in the proposed PBS population. The PBAC recalled its previous advice that the biases and the transitivity issues with the indirect comparison indicated that the incremental effectiveness of crizotinib over pemetrexed was overestimated in the submission. However, the Committee was satisfied that the incremental effectiveness of crizotinib treatment in the ROS1-positive NSCLC population would be similar to that in the ALK-positive NSCLC population (paragraph 7.9, November 2017 PBAC PSD). The PBAC advised that there was neither any new evidence nor any compelling justifications in the minor resubmission that was likely to necessitate any change to its previous interpretation of the clinical evidence.
- 6.6 The PBAC noted that the minor resubmission presented a respecified base case ICER of \$45,000/QALY - \$75,000/QALY (compared to \$45,000/QALY - \$75,000/QALY in the November 2017 submission) by addressing the PBAC's concerns surrounding (i) the efficacy of the comparator, pemetrexed (outcomes in the comparator arm were increased by a factor of ■■■); (ii) the incremental effectiveness of crizotinib versus pemetrexed (time horizon was reduced from 10 to 5 years); and (iii) pemetrexed cost offsets (updated to reflect the current PBS prices). The PBAC noted that changing these factors together with the DPMQ proposed in the November 2017 submission resulted in an ICER of \$75,000/QALY - \$105,000/QALY. A reduction of ■■■% (\$■■■ to \$■■■) to the proposed DPMQ of crizotinib for the ROS1 population reduced the ICER to the respecified base case of \$45,000/QALY - \$75,000/QALY. The PBAC considered that the changes made to the economic model to address the Committee's previous concerns were reasonable, and the advised that the resultant ICER was high but acceptable at the price proposed in the minor resubmission, noting the unmet clinical need in a small patient population.
- 6.7 The PBAC noted that the minor resubmission requested a single weighted average

effective price across the two reimbursed populations of NSCLC patients and claimed that this would simplify the Special Pricing Arrangements and associated contractual requirements. The PBAC noted that by applying a [REDACTED]:[REDACTED] ratio across the ALK (effective AEMP = \$ [REDACTED]) and ROS1 (effective AEMP = \$ [REDACTED]) indications, the minor resubmission proposed that crizotinib be listed at the proposed effective AEMP of \$ [REDACTED]. The PBAC considered that this was reasonable.

- 6.8 The PBAC advised that the utilisation assumptions supporting the financial estimates were reasonable from a PBS perspective after adjusting the estimate of eligible patients in the first year to include patients who would receive treatment under the proposed grandfathering arrangement.
- 6.9 The PBAC maintained that given the modest financial estimates in a relatively small population, a risk sharing arrangement would not be necessary.
- 6.10 The PBAC advised that the Early Supply Rule should not apply to the listing of crizotinib.
- 6.11 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* that crizotinib should not be treated as interchangeable on an individual patient basis with any other drugs.
- 6.12 The PBAC advised that crizotinib is not suitable for prescribing by nurse practitioners.
- 6.13 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item:

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

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
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Condition:	Non-small cell lung cancer
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have a WHO performance status of 2 or less.
Population criteria:	Patient must have evidence of ROS1 gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.
Prescriber instructions:	The authority application must be made in writing and must include: (3) A completed authority prescription form; and (4) A completed ROS1-Positive Non-Small-Cell Lung Cancer Authority Application – Supporting Information Form, which includes details of ROS1 gene rearrangement in tumour material.
Administrative advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
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Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.</p>
Prescriber instructions:	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
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Treatment phase:	Grandfathering treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

Clinical criteria:	<p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [PBS listing date],</p> <p>AND</p> <p>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC,</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>Patients may qualify for PBS-subsidised treatment under this restriction once only.</p>
Population criteria:	<p>Patient must have evidence of ROS1 gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.</p>
Prescriber instructions:	<p>The authority application must be made in writing and must include:</p> <p>(3) A completed authority prescription form; and</p> <p>(4) A completed ROS1-Positive Non-Small-Cell Lung Cancer Authority Application – Supporting Information Form, which includes details of ROS1 gene rearrangement in tumour material.</p>
Administrative advice:	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

8 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.

9 Sponsor's Comment

Pfizer welcomes the PBAC's recommendation to make crizotinib available for the treatment of advanced ROS1-positive non-small cell lung cancer; a rare disease with high unmet clinical need.