

**6.09 CRIZOTINIB,  
Capsule 200 mg,  
Capsule 250 mg,  
Xalkori<sup>®</sup>, Pfizer Australia Pty Ltd**

**1 Purpose of Application**

- 1.1 To inform the PBAC of the outcome of the crizotinib managed entry scheme (MES) for the treatment of patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) as part of the requirements of the MES.
- 1.2 To request changes to the PBS restriction for crizotinib as a result of the MES conclusion.

**2 Requested listing**

- 2.1 The submission requested that the restriction be amended to remove the requirement for patients to be registered for the MES. The submission also noted that the grandfather restriction could now also be removed. No other changes to the restriction were proposed.
- 2.2 The grandfather restriction was last accessed on 14 September 2015, therefore it is likely all patients who were eligible to access crizotinib under this restriction have since moved onto PBS-subsidised treatment.
- 2.3 The proposed deletions to the existing listing are shown in strikethrough:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
CRIZOTINIB					
crizotinib 200 mg capsule, 60	1	1	\$7276.18	Xalkori <sup>®</sup>	Pfizer
crizotinib 250 mg capsule, 60	1	1			Australia Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	
<b>Severity:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic)
<b>Condition:</b>	non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
<b>Treatment phase:</b>	Initial treatment

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<b>Restriction Method:</b>	<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
<b>Clinical criteria:</b>	<p>The treatment must be as monotherapy,</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>
<b>Population criteria:</b>	<p>Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.</p>
<b>Prescriber Instructions</b>	<p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed ALK-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form, which includes details of ALK gene rearrangement in tumour material by FISH testing.</p>
<b>Administrative advice</b>	<p>Special Pricing Arrangements apply.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p> <p><b>MANAGED ENTRY SCHEME</b></p> <p><del>This medicine has been listed on the PBS via a Managed Entry Scheme (MES). This MES provides a mechanism to address the uncertainty over the size of the additional clinical benefit of this medicine while providing early access to those patients for whom there is a high clinical need.</del></p> <p><del>Information about the benefits of this medicine in clinical practice will be collected, analysed and presented to the Pharmaceutical Benefits Advisory Committee (PBAC) for consideration in the near future.</del></p>

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	<p>Prescribers and patients must be aware that if a drug listed via a MES does not prove as beneficial in clinical practice as appeared in the clinical data presented to the PBAC, it may subsequently have its restriction modified, or may be removed from the PBS by the Commonwealth or at the request of the sponsor.</p> <p>The relevant information for crizotinib is being collected about selected patients from their prescribing doctor. Patients are being selected on the grounds that they are crizotinib-naïve when initiating PBS supply. Selection will stop when there are enough patients providing the relevant information.</p> <p>Details of these arrangements are included in an information sheet that must be provided by the prescribing doctor to each selected patient receiving PBS subsidy for this medicine.</p> <p>For more information on Managed Entry Schemes, please visit <a href="http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-pbac-submissions">http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-pbac-submissions</a>.</p> <p>For more information on the PBAC's consideration of this medicine and its MES, please visit <a href="http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014">http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014</a></p>
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<b>Episodicity:</b>	
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<b>Condition:</b>	non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The treatment must be as monotherapy,  AND  Patient must have previously been issued with an authority prescription for this drug,  AND  Patient must not have progressive disease.
<b>Administrative advice</b>	Special Pricing Arrangements apply.  Prescribers must provide the patient's unique identifier (in form XALK XXX, where XXX is a numerical value) when requesting PBS Authority approval. The patient's unique identifier was received upon registering the patient with the sponsor's

	<p>erizotinib (Xalkori) Managed Entry Scheme website at the time of initiation.</p> <p>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).</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p><b>MANAGED ENTRY SCHEME</b></p> <p><del>This medicine has been listed on the PBS via a Managed Entry Scheme (MES). This MES provides a mechanism to address the uncertainty over the size of the additional clinical benefit of this medicine while providing early access to those patients for whom there is a high clinical need.</del></p> <p><del>Information about the benefits of this medicine in clinical practice will be collected, analysed and presented to the Pharmaceutical Benefits Advisory Committee (PBAC) for consideration in the near future.</del></p> <p><del>Prescribers and patients must be aware that if a drug listed via a MES does not prove as beneficial in clinical practice as appeared in the clinical data presented to the PBAC, it may subsequently have its restriction modified, or may be removed from the PBS by the Commonwealth or at the request of the sponsor.</del></p> <p><del>The relevant information for crizotinib is being collected about selected patients from their prescribing doctor. Patients are being selected on the grounds that they are crizotinib-naïve when initiating PBS supply. Selection will stop when there are enough patients providing the relevant information.</del></p> <p><del>Details of these arrangements are included in an information sheet that must be provided by the prescribing doctor to each selected patient receiving PBS subsidy for this medicine.</del></p> <p><del>For more information on Managed Entry Schemes, please visit <a href="http://www.pbs.gov.au/info/publication/factsheets/shared/framework">http://www.pbs.gov.au/info/publication/factsheets/shared/framework</a> for introduction of managed entry scheme for PBAC submissions.</del></p> <p><del>For more information on the PBAC's consideration of this medicine and its MES, please visit <a href="http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib_psd_11-2014">http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib_psd_11-2014</a></del></p>
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For more detail on PBAC's view, see section 6 "PBAC outcome".

### 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). Crizotinib was processed as a co-dependent submission, with an application for ALK mutation testing submitted to the Medical Services Advisory Committee (MSAC).
- 3.2 At its November 2014 meeting, the PBAC recommended the Authority required listing of crizotinib for the treatment of patients with ALK-positive, advanced NSCLC. The PBAC considered that the incremental overall survival (OS) gain of 12.0 months based on the comparison arms from non-exchangeable trials was inappropriate and likely to overestimate the comparative treatment effect of crizotinib. The PBAC considered that the more likely OS gain is either 3.1 months (in line with the projection based on the meta-regression by Johnson et al 2006) or 3.5 months (in line with the more conservative results of the methods of adjusting for crossover). The PBAC considered that a MES would be appropriate and provide a mechanism to address the uncertainty related to the magnitude of clinical benefit, while providing early access to patients for whom there is a high clinical need.
- 3.3 Crizotinib was listed on the PBS on 1 July 2015.

### 4 Managed Entry Scheme Framework

- 4.1 The Crizotinib MES was designed to collect survival data for the first 50 crizotinib-naïve patients to receive crizotinib after PBS listing, to compare to the survival outcomes of the phase III clinical trial (A8081007). The sample size of 50 was proposed based on the expectation that, with the estimated number of incident patients, it would take approximately two years to generate the data. Under the Deed of Agreement, the company was required to report on the mortality status of each patient for 12 months following their first PBS-subsidised supply of crizotinib. The MES concluded on 13 December 2016 with completion of the follow-up period on the 50<sup>th</sup> patient on the MES. The company's obligations are listed under clauses in Attachment B.2 of the Deed. A summary of the clauses in Attachment B.2 of the Deed is provided in Table 1 below.

**Table 1: Summary of obligations in the Deed of Agreement**

<b>Obligations under Attachment B.2 of the Deed</b>	<b>Comment on submission</b>
Establish the MES Data collection, which is to determine the Alive Status of all MES Patients	Complied with the Deed. Data collection process was developed in collaboration with the Department.
Submit a report on the outcomes of the MES Data Collection to the Department as soon as possible and in any event no later than the end of the consecutive period of fourteen months commencing on the Completed Enrolment Date.	Complied with the Deed.
Manage and administer the MES Data Collection, including building and maintaining the website and associated database.	Complied with the Deed. A third party was contracted to run the MES including building and maintaining the website and associated database.
<b>Obligations under Attachment B.2 of the Deed related to the management and administration of the MES Data Collection</b>	

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Obligations under Attachment B.2 of the Deed	Comment on submission
Inform all Oncologists about the MES Data Collection and the need for Oncologists to register their patient in order to obtain a unique identifier to be included in the authority required form.	Complied with the Deed. The third party was responsible for liaising with the Oncologists.
Communicate to all Oncologists providing information required in order to register a patient and link to the MES Data Collection website.	
Provide the Oncologists with the unique identifier for each MES, which is to be used by the Oncologist to seek authority for the initial script from the Human Services Department.	
Provide information to the Pharmacy with directions on how to complete the information on the website required under the MES Data Collection.	Complied with the Deed. The third party was responsible for liaising with the Pharmacists
Contact the Pharmacy for date of dispensing of the Drug to an MES Patient where no date is provided at the time of dispensing	
Provide the Department with monthly recruitment reports of MES Patients, that will present: <ul style="list-style-type: none"> <li>i. the unique identifier;</li> <li>ii. the date of dispensing; and</li> <li>iii. whether the MES Patient has consented.</li> </ul> for corroboration with the Human Services Department data and for agreement on the 50 MES Patients and their dispensing date.	Complied with the Deed. Additionally, the sponsor and pharmaceutical advisor reached consensus on eligibility prior to each patient's survival status being known.
Use best endeavours to make regular contact with Oncologists to determine the status of the 50 MES Patients to minimise risk of not finding out the final status of any of the MES Patients.	Complied with the Deed. The third party contacted the Oncologists once per quarter to enquire about patient survival status.
Provide the Department with monthly survival reports for the MES Patients, once the first MES Patient has been followed for 12 months. This report will include details of the: <ul style="list-style-type: none"> <li>i. unique identifier and initials of the MES Patients;</li> <li>ii. date of dispensing; and</li> <li>iii. date of death or confirmation of survival.</li> </ul> for corroboration with the Human Services Department records.	Complied with the Deed. The minor submission includes the final survival report.
Close the website for the MES Data Collection once the final report has been presented to the Department, and once the Human Services Department authority required form has been amended to remove the need for a unique identifier in order for Oncologists to prescribe the Drug.	Complied with the Deed.

Source: crizotinib MES Deed of Agreement

- 4.2 According to the Deed, the company was required to rebate the Commonwealth a pre-specified percentage depending on the survival rate of MES patients 12 months after initiating treatment with crizotinib from the MES data collection.
- 4.3 The MES rebate percentage based on the proportion of the first 50 consecutive PBS patients starting on crizotinib who are observed to be alive at 12 months are presented in Table 2 below. The threshold of 68.9% survival corresponding to a

0.00% rebate is the estimate of the proportion of patients alive after 12 months modelled from the A8081007 trial.

**Table 2: MES rebate percentages**

Survival rate of MES patients 12 months after initiating treatment with crizotinib from the MES data collection	MES rebate percentage
68.9% or more	0.00%
67.9%-68.8%	%
66.9%-67.8%	%
65.9%-66.8%	%
64.9%-65.8%	%
63.9%-64.8%	%
62.9%-63.8%	%
61.9%-62.8%	%
60.9%-61.8%	%
59.9%-60.8%	%
58.9%-59.8%	%
57.9%-58.8%	%
56.9%-57.8%	%
55.9%-56.8%	%
54.9%-55.8%	%
53.9%-54.8%	%
52.9%-53.8%	%
51.9%-52.8%	%
50.9%-51.8%	%
49.9%-50.8%	%
48.9%-49.8%	%
48% or less	%

Source: crizotinib MES Deed of Agreement

- 4.4 As the initial MES entry price of crizotinib was as requested by the sponsor in the March 2014 submission, relying on the base case ICER of \$45,000/QALY - \$75,000/QALY, the price of crizotinib would either be maintained or reduced depending on the outcome of the MES with no option of a higher price.

## 5 Consideration of the 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 that no consumer comments were received for this item.

### *Outcomes of the crizotinib MES*

- 5.3 The XALK registration numbers for the first 50 treatment-naïve patients to receive crizotinib are not sequential from 1 to 50 because some registration numbers were used for testing purposes; [REDACTED]

- [REDACTED]
- 5.4 The MES data provided by the sponsor was cross-checked against Department of Human Services (DHS) fact-of-death data. No discrepancies between mortality status reported by the MES and collected by DHS were detected. [REDACTED]

- 5.5 [REDACTED]. However, the reason for cessation of PBS-subsidised crizotinib (e.g. disease progression, trial enrolment, etc) was not available. Analysis of post-crizotinib PBS-subsidised treatments has not been undertaken at this time.

- 5.6 [REDACTED] In all cases, at least 12 months' follow-up data were available from the later of the two dates of commencement; therefore these discrepancies did not affect the survival analysis.

- 5.7 The data from the MES indicate a survival percentage at 12 months of 70%. The MES rebate percentages from the Deed of Agreement (see table 2 above) range from a 0% rebate for a survival percentage of 68.9% or above, to a [REDACTED] % rebate for a survival percentage of 48% or less.

- 5.8 The PBAC noted that the data from the MES provided by the sponsor indicated survival at 12 months of 70%. The PBAC also noted there were no issues raised when the MES data was cross-checked against DHS fact-of-death data. On this basis, the PBAC considered that the requirements for the MES had been met, and no rebate was required.

*For more detail on PBAC's view, see section 6 "PBAC outcome".*

**Department's observations on the crizotinib MES process**

- 5.9 Each MES carries the potential that the clinical benefit indicated in the early data will not be substantiated by analysis of further data. All stakeholders (sponsor, patients, prescribers and the Commonwealth) must be mindful of the possibility that such a situation may lead to the removal of the drug from the PBS (either by the Commonwealth or at the request of the sponsor), or to changes in the restriction criteria. Under the crizotinib MES, this advice was communicated via the PBS restriction wording and the PBS Authority application form. In addition, the sponsor was required under the terms of the MES to inform prescribers in writing of the MES data collection requirements.

- 5.10 The extent to which patients understood the implications of the crizotinib MES was unknown, although the written application process required that patients signify their understanding that "...crizotinib has been listed on the PBS via the Managed Entry Scheme and my prescriber has explained the details of these arrangements to me."
- 5.11 The extent to which oncologists understood the implications of the crizotinib MES was unknown. The PBS application form for crizotinib required that prescribers signify their acknowledgement that they have explained to their patient "...the circumstances governing PBS subsidised treatment with crizotinib, including the arrangements governing the Managed Entry Scheme."
- 5.12 The process of collecting PBS data for the purpose of administering an MES arrangement was an unfamiliar one for PBS prescribers. [REDACTED]
- 5.13 Examination of individual de-identified patient applications by the Department was required to determine whether ALK testing was performed before or after the PBS listing of crizotinib, and therefore whether patients were naïve or experienced to treatment. Patients whose ALK rearrangement was confirmed after 1 July 2015 were determined to be crizotinib naïve and were included in the analysis. Patients whose ALK test was performed prior to 1 July 2015 were determined to be crizotinib-experienced and were excluded from the analysis.
- 5.14 PBS prescribers may be unaware of the pivotal nature of the MES arrangements in allowing the PBAC to make a positive recommendation for crizotinib, nor of the importance of their role in accurately reporting patients' treatment status to the MES registry. Direct engagement with relevant peak professional organisations may be considered in future to ensure that prescribers have clarity on the terms of the MES and the importance of reliable reporting in supporting future MES arrangements.
- 5.15 Although the date of ALK testing provided an objective means of determining whether patients were crizotinib-naïve or –experienced, without this additional information, the determination of treatment status would have rested on the prescriber's declaration upon registry enrolment. [REDACTED] The potential implications of misreported data must be considered for future MES arrangements - if the crizotinib PBS listing did not require a diagnostic test with the written Authority application, the reliability of the survival analysis could have been compromised.
- [REDACTED]

- 5.16 Publishing MES terms in Public Summary Documents (PSDs) – in its advice on the crizotinib MES, the PBAC stated unequivocally in its ratified Minutes that information relating to the terms of the MES should be placed in the public domain. This provided important public context for the PBAC’s recommendation. When considering future MES arrangements, the PBAC should continue to make similar statements in its PSDs about what MES-related information is required.
- 5.17 Managing discrepancies – in the case of the crizotinib MES, there was concordance between the registry and the PBS data set with regard to survival status. Although some minor differences were observed in dates of death, these did not result in a different conclusion for the analysis. This highlights the need for clarity at the outset of the MES about which data set would take precedence (sponsor registry or PBS data) in the event of a discrepancy.
- 5.18 Scaling MES arrangements to larger populations – the crizotinib MES required substantial work from both the Department and the sponsor to correctly identify crizotinib-naïve patients. As noted above, this required examination of individual patient applications to determine the date of ALK testing. This manual nature of the work and the time taken to complete it were not anticipated at the commencement of the MES, particularly considering that only 50 patients were to be included in the analysis. The issues of scaling this work up to larger populations should be taken into account in developing future MES arrangements that require collection of PBS data.
- 5.19 Written Authority vs. telephone or Streamlined Authority – the crizotinib written Authority listing facilitated the following important elements of the MES:
- Data quality – having written applications for later referral allowed validation of the data. This would have not been possible with a telephone or Streamlined Authority;
  - Patient and prescriber consent – all written PBS Authority application require that both prescriber and patient acknowledge that the PBS listing criteria are understood. The PBS Authority application form for crizotinib also required acknowledgement that the data collection requirements of the MES were agreed.
- Although the written Authority process may be considered onerous by prescribers, crizotinib’s written application was pivotal to the administration of the MES. The PBAC may wish to consider a written application process for future MES arrangements requiring PBS data collection.
- 5.20 Patients declining to participate in the MES registry – no patients who received crizotinib declined to participate in the registry, however an allowance was made for any such patients to still receive crizotinib on the PBS. Future MES arrangements involving collection of PBS data will need to take into account the possibility of patients that meet the PBS clinical criteria but who conscientiously object to being enrolled in the MES registry.

*For PBAC’s view, see section 6 “PBAC outcome”.*

**Department's suggestions on factors to consider in future MES arrangements**

- 5.21 The following matters may be considered in future MES arrangements with a PBS data collection component:
- Feasibility of scaling MES data collection to larger populations;
  - Maximum possible transparency about the terms of the MES and the possible implications of the MES not substantiating the initial claims for the drug;
  - Allowance for patients to conscientiously object to registry enrolment and still receive the drug on the PBS;
  - Written application process to provide best opportunity for collection of accurate data and patient/prescriber acknowledgement;
  - Direct engagement with peak bodies representing prescribers to emphasise the importance of accurate data collection;
  - Availability of other objective data sources to validate registry data and resolve discrepancies or patients lost to follow up;
  - Up-front agreement with sponsor on which data sources take priority in event of discrepancy.
- 5.22 Fact-of-death data were reported by the Department of Human Services (DHS) as part of the specific arrangements for the PBS listing for crizotinib and were instrumental in validating the sponsor's MES registry data. Reliable survival data may be highly informative in future analyses of PBS utilisation patterns, including those undertaken by the Drug Utilisation Subcommittee. The PBAC may wish to consider advising the Department to undertake discussions with DHS about obtaining fact-of-death data for all PBS-listed drugs as part of standard, ongoing reports.

*For PBAC's view, see section 6 "PBAC outcome".*

**6 PBAC Outcome**

- 6.1 The PBAC recommended that the restrictions for crizotinib for Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) be amended to remove the requirement that patients are registered for the Managed Entry Scheme (MES), including the associated notes, on the basis that the requirements of the MES had been satisfied.
- 6.2 The PBAC noted the outcome of the MES data collection that 70% (35 out of 50 patients) of patients had survived at 12 months follow-up from the date of their first dispensing of PBS-subsidised crizotinib. The PBAC noted that this survival outcome was consistent with the 68.9% survival estimated for the phase III clinical trial (A8081007) and, in accordance with the Deed of Agreement, allows crizotinib to continue to be listed at the initial MES entry price. The PBAC considered that the sponsor had fulfilled the requirements of the crizotinib Deed of Agreement with respect to the MES, and therefore considered that the crizotinib MES could be concluded.

- 6.3 Accordingly, the PBAC recommended that the current crizotinib listing be amended to remove the requirement for patients to be registered for the MES. Further, the PBAC noted that all patients who were eligible under the grandfathering treatment restriction would now have moved onto PBS-subsidised treatment, and therefore considered it appropriate to remove the grandfathering treatment restriction.
- 6.4 The PBAC noted that ceritinib, which is currently PBS-listed for the same eligible population at the same published price as crizotinib, has a telephone authority, whereas crizotinib has a written authority. However, the PBAC also recalled that it has not considered evidence regarding the comparative efficacy, safety, and cost-effectiveness of crizotinib and ceritinib. The PBAC therefore considered that crizotinib should remain as a written authority until this therapeutic relativity can be established via a minor submission from the sponsor of crizotinib.
- 6.5 The PBAC noted that the crizotinib MES process raised a number of considerations for future MES arrangements involving PBS patient data collection. In particular, the PBAC noted the significant resources required for both the sponsor and the Department to examine individual patient applications in order to correctly identify the first 50 crizotinib-naïve patients for the crizotinib MES. The PBAC noted that this would be an important consideration for the development of future MES arrangements, particularly those that which involve identifying and collecting data on a larger population of patients. The PBAC also noted the importance of maximising the participation of all eligible patients receiving PBS-subsidy to ensure the reliability of the data collected for the MES.
- 6.6 The PBAC considered that fact-of-death data collected by DHS was an informative and reliable source of survival data that, in addition to providing an important validation tool for the prescriber-reported survival data, would also be useful in analysing PBS drug utilisation data more broadly. However, the PBAC noted that overall survival would not always be a relevant outcome measure, so future MES arrangements may instead need to report other types of patient-relevant outcome.
- 6.7 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 Amend existing listing as follows:

The proposed deletions to the existing listing are shown in strikethrough:

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crizotinib 250 mg capsule, 60	1	1		Australia Pty Ltd

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<b>Population criteria:</b>	Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.
<b>Prescriber Instructions</b>	The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed ALK-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form, which includes details of ALK gene rearrangement in tumour material by FISH testing.
<b>Administrative advice</b>	Special Pricing Arrangements apply.  Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).  Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a>  Applications for authority to prescribe should be forwarded to:

	<p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p> <p><b>MANAGED ENTRY SCHEME</b></p> <p>This medicine has been listed on the PBS via a Managed Entry Scheme (MES). This MES provides a mechanism to address the uncertainty over the size of the additional clinical benefit of this medicine while providing early access to those patients for whom there is a high clinical need.</p> <p>Information about the benefits of this medicine in clinical practice will be collected, analysed and presented to the Pharmaceutical Benefits Advisory Committee (PBAC) for consideration in the near future.</p> <p>Prescribers and patients must be aware that if a drug listed via a MES does not prove as beneficial in clinical practice as appeared in the clinical data presented to the PBAC, it may subsequently have its restriction modified, or may be removed from the PBS by the Commonwealth or at the request of the sponsor.</p> <p>The relevant information for crizotinib is being collected about selected patients from their prescribing doctor. Patients are being selected on the grounds that they are crizotinib-naïve when initiating PBS supply. Selection will stop when there are enough patients providing the relevant information.</p> <p>Details of these arrangements are included in an information sheet that must be provided by the prescribing doctor to each selected patient receiving PBS subsidy for this medicine.</p> <p>For more information on Managed Entry Schemes, please visit <a href="http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-pbac-submissions">http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-pbac-submissions</a>.</p> <p>For more information on the PBAC's consideration of this medicine and its MES, please visit <a href="http://www.pbs.gov.au/info/industry/listing/clements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014">http://www.pbs.gov.au/info/industry/listing/clements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014</a></p>
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<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic)
<b>Condition:</b>	non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
<b>Treatment phase:</b>	Continuing treatment

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<p><b>Restriction Level / Method:</b></p>	<p><input type="checkbox"/> Restricted benefit  <input checked="" type="checkbox"/> Authority Required - In Writing  <input checked="" type="checkbox"/> Authority Required - Telephone  <input checked="" type="checkbox"/> Authority Required – Emergency  <input checked="" type="checkbox"/> Authority Required - Electronic  <input type="checkbox"/> Streamlined</p>
<p><b>Clinical criteria:</b></p>	<p>The treatment must be as monotherapy,  AND  Patient must have previously <del>been issued with an authority prescription received</del> <i>PBS-subsidised treatment with for this drug for this condition</i>  AND  Patient must not have progressive disease.</p>
<p><b>Administrative advice</b></p>	<p>Special Pricing Arrangements apply.</p> <p><del>Prescribers must provide the patient's unique identifier (in form XALK XXX, where XXX is a numerical value) when requesting PBS Authority approval. The patient's unique identifier was received upon registering the patient with the sponsor's erizotinib (Xalkori) Managed Entry Scheme website at the time of initiation.</del></p> <p>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).</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services  Complex Drugs  Reply Paid 9826  HOBART TAS 7001</p> <p><b>MANAGED ENTRY SCHEME</b></p> <p><del>This medicine has been listed on the PBS via a Managed Entry Scheme (MES). This MES provides a mechanism to address the uncertainty over the size of the additional clinical benefit of this medicine while providing early access to those patients for whom there is a high clinical need.</del></p> <p>Information about the benefits of this medicine in clinical practice will be collected, analysed and presented to the Pharmaceutical Benefits Advisory Committee (PBAC) for consideration in the near future.</p>

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	<p>Prescribers and patients must be aware that if a drug listed via a MES does not prove as beneficial in clinical practice as appeared in the clinical data presented to the PBAC, it may subsequently have its restriction modified, or may be removed from the PBS by the Commonwealth or at the request of the sponsor.</p> <p>The relevant information for crizotinib is being collected about selected patients from their prescribing doctor. Patients are being selected on the grounds that they are crizotinib-naïve when initiating PBS supply. Selection will stop when there are enough patients providing the relevant information.</p> <p>Details of these arrangements are included in an information sheet that must be provided by the prescribing doctor to each selected patient receiving PBS subsidy for this medicine.</p> <p>For more information on Managed Entry Schemes, please visit <a href="http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-pbac-submissions">http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-pbac-submissions</a>.</p> <p>For more information on the PBAC's consideration of this medicine and its MES, please visit <a href="http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014">http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014</a></p>
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7.2 Delete item:

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	
<b>Severity:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic)
<b>Condition:</b>	non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
<b>Treatment phase:</b>	Grandfathering treatment
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	<p>Patient must have received treatment with crizotinib for this condition prior to 1 July 2015,</p> <p>AND</p> <p>The treatment must be as monotherapy,</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>

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	Patient must have a WHO performance status of 2 or less.
<b>Population criteria:</b>	Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.
<b>Prescriber Instructions:</b>	The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed ALK-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form, which includes details of ALK gene rearrangement in tumour material by FISH testing.
<b>Administrative advice</b>	<p>Special Pricing Arrangements apply.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p><b>MANAGED ENTRY SCHEME</b></p> <p>This medicine has been listed on the PBS via a Managed Entry Scheme (MES). This MES provides a mechanism to address the uncertainty over the size of the additional clinical benefit of this medicine while providing early access to those patients for whom there is a high clinical need.</p> <p>Information about the benefits of this medicine in clinical practice will be collected, analysed and presented to the Pharmaceutical Benefits Advisory Committee (PBAC) for consideration in the near future.</p> <p>Prescribers and patients must be aware that if a drug listed via a MES does not prove as beneficial in clinical practice as appeared in the clinical data presented to the PBAC, it may subsequently have its restriction modified, or may be removed from the PBS by the Commonwealth or at the request of the sponsor.</p> <p>The relevant information for crizotinib is being collected about selected patients from their prescribing doctor. Patients are being selected on the grounds that they are crizotinib-naive when initiating PBS supply. Selection will stop when there are enough patients providing the relevant information.</p> <p>Details of these arrangements are included in an information sheet that must be provided by the prescribing doctor to each selected patient receiving PBS-subsidy for this medicine.</p> <p>For more information on Managed Entry Schemes, please visit <a href="http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-">http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-</a></p>

	<p>of-managed-entry-scheme-for-PBAC-submissions.</p> <p>For more information on the PBAC's consideration of this medicine and its MES, please visit <a href="http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014">http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014</a></p>
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## **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 is very pleased with the successful conclusion of the managed entry scheme for crizotinib. By entering into a managed entry scheme, crizotinib was made available to a group of patients with a high clinical need, while addressing a key area of uncertainty for the PBAC. The managed entry scheme confirmed the original estimate from the clinical trial, through the collection of real-world Australian data. Pfizer acknowledges and thanks the patients, oncologists and pharmacists who made the data collection possible and the Department of Health for actively supporting resolution of the data queries.