

**5.03 CERITINIB,
Capsule 150 mg,
Zykadia[®],
Novartis Pharmaceuticals Australia Pty Ltd.**

1 Purpose of Application

1.1 The submission requested a General Schedule Authority Required listing for ceritinib for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on a prior ALK inhibitor (ALKi).

2 Requested listing

2.1 The restriction proposed by the sponsor is provided below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
CERITINIB ceritinib 150 mg capsule, 30 50	150		1	\$ [REDACTED] (Published) \$ [REDACTED] (Effective)	Zykadia	Novartis Pharmaceuticals Australia Pty Ltd

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 checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

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Clinical criteria:	<p>Patient must not have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have a WHO performance status of 2 or less; AND The condition must have progressed following treatment with crizotinib Patient must have disease progression following treatment with an anaplastic lymphoma kinase inhibitor (ALKi); OR Patient must have developed intolerance to crizotinib of a severity necessitating permanent treatment withdrawal AND Patient must have provided evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement prior to treatment with an ALKi; AND The treatment must be the sole PBS-subsidised therapy for this condition as monotherapy;</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>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
Episodicity:	-
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 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
Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition as monotherapy; AND Patient must have previously been issued with an authority prescription for this drug for this condition; AND Patient must not have progressive have stable or responding disease</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

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Name, Restriction, Manner of administration and form	Max. Qty	№.of Units Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
CERITINIB ceritinib 150 mg capsule, 30 50	150	1	\$7275.17 (Published) \$ [REDACTED] (Effective)	Zykadia Novartis Pharmaceuticals Australia Pty Ltd

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 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
Clinical criteria:	<p>Patient must have <i>previously</i> received <i>non-PBS subsidised treatment</i> with this drug <i>for this condition</i> prior to [PBS listing date]; AND <i>The condition must have progressed following treatment with crizotinib</i> Patient must have disease progression following treatment with an anaplastic lymphoma kinase inhibitor (ALKi); OR <i>Patient must have developed intolerance to crizotinib of a severity necessitating permanent treatment withdrawal</i> AND Patient must have provided evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement prior to treatment with an ALKi; AND <i>The treatment must be the sole PBS-subsidised therapy for this condition as monotherapy;</i> AND Patient must not have progressive <i>have stable or responding disease</i></p>
Administrative Advice	<p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p>

2.2 The submission sought listing on the basis of a cost-minimisation analysis of ceritinib compared with platinum doublet chemotherapy followed by pemetrexed maintenance.

For more details on PBAC's view, see section 7 "PBAC Outcome".

3 Background

- 3.1 Ceritinib was TGA registered on 31 March 2016 for the following indication:
“as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant of crizotinib.”
- 3.2 This is the first consideration of ceritinib by the PBAC.

For more details on PBAC’s view, see section 7 “PBAC Outcome”.

4 Clinical place for the proposed therapy

- 4.1 *ALK* rearrangements are found in approximately 3-5% of cases of NSCLC and define a distinct molecular subtype of lung cancer. Ceritinib is an oral, second-generation ALKi that directly targets the ALK protein and acts as a tyrosine kinase inhibitor to inhibit autophosphorylation of ALK and ALK-mediated phosphorylation of downstream signalling proteins.

5 Comparator

- 5.1 The submission nominated platinum doublet chemotherapy (carboplatin or cisplatin with gemcitabine for up to 4 cycles) followed by pemetrexed maintenance until progression as the main comparator.

For more details on PBAC’s view, see section 7 “PBAC Outcome”.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (18) and organisations (3) via the Consumer Comments facility on the PBS website.
- 6.3 The comment from Rare Cancers Australia noted that ceritinib would make a big difference in the quality of life of patients who progress on crizotinib. The advice received from the Lung Foundation placed emphasis on ceritinib being an effective option for second-line treatment of patients with *ALK* positive NSCLC, particularly those with brain metastases. The Medical Oncology Group of Australia (MOGA) advised that, in its view, ceritinib was of considerable clinical value due to its high level of activity in heavily pre-treated patients and modest level of toxicity. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.4 The key evidence provided in the submission was one randomised head-to-head open-label trial comparing ceritinib to chemotherapy (pemetrexed or docetaxel, at the discretion of the investigators) over approximately 10 months (n=231, ceritinib n=115, chemotherapy n=116). The submission relied upon a sub-group analysis of patients who received pemetrexed (pemetrexed n=█) in comparison with ceritinib, to establish the claim of non-inferiority of ceritinib over pemetrexed. The evaluation noted that the allocation to pemetrexed or docetaxel in the control arm was not stratified and it is unclear whether confounding influenced the results. The subgroup analysis was not pre-specified in the protocol.
- 6.5 Details of the trial presented in the submission are provided in the table below.

Table 1 Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
ASCEND-5	A Phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib. First Available Results (FAR) Primary analysis. 7 June 2016.	FAR: 7 June 2016
	Clinical Trial Protocol. A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib. 23 April 2015.	Protocol 23 April 2015

Source: Table 8, p42 of the submission.

- 6.6 The key features of the direct randomised trial are summarised in the table below.

Table 2 Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome
ceritinib vs. chemotherapy					
ASCEND-5	231	R, OL Median █ mths (ceritinib arm) █ mths (chemo arm)	Low/high*	Failed chemo and crizotinib	PFS
ceritinib vs. pemetrexed					
Subgroup of ASCEND-5	█	NR, OL Median █ mths (ceritinib arm) █ mths (pemetrexed arm)	High**	Failed chemo and crizotinib	PFS

R=randomised, NR = not randomised; OL=open label; PFS=progression-free survival; mths = months; chemo = chemotherapy.

* For the primary endpoint of PFS, the overall risk of bias is low, given that it was determined by a blinded independent review committee (BIRC). However, due to the open-label design of the study, patient reported outcome measures may be subject to bias.

** Since the allocation to pemetrexed was not randomised and the subgroup analysis was not pre-specified in the protocol, the analysis was subject to high risk of bias.

Source: compiled during the evaluation

- 6.7 Ceritinib was used as a 3rd or fourth line therapy in ASCEND-5. The evaluation noted that the comparator in the trial (docetaxel or pemetrexed) did not directly match the submission's proposed comparator of platinum chemotherapy followed by pemetrexed maintenance.

- 6.8 The submission relied upon blinded independent review committee (BIRC) determined progression-free survival (PFS), the primary outcome in the ASCEND-5 trial, to determine non-inferiority of ceritinib over pemetrexed. The evaluation noted that it remains uncertain whether PFS is an appropriate surrogate for overall survival (OS) in NSCLC^a. The results of OS were confounded due to a considerable proportion of patients in the control arm switching to ceritinib after progression on chemotherapy.
- 6.9 Patient reported outcome questionnaires (EORTC QLQ-C30/LC13, Lung Cancer Symptom Scale (LCSS) and EQ-5D) were collected at baseline, during treatment and up until progression (even if treatment was stopped prior).

Comparative effectiveness

- 6.10 The difference in median PFS for the full analysis set is 3.8 months and 5.1 months when progression is determined by BIRC and investigators, respectively. In both BIRC and investigator analyses, the hazard ratio (HR) favours ceritinib and is statistically significant (Table 3).

Table 3 Results of progression free survival (BIRC and Investigator) for the full analysis set in ASCEND-5

	Ceritinib		Chemotherapy		Diff. in medians	Hazard ratio (95% CI) Log rank p value
	n/N with event (%)	Median months to event (95% CI)	n/N with event (%)	Median months to event (95% CI)		
BIRC	83/115 (72.2)	5.4 (4.1, 6.9)	89/116 (76.7)	1.6 (1.4, 2.8)	3.8	0.49 (0.36, 0.67) p<0.001
Investigator	83/115 (72.2)	6.7 (4.4, 7.9)	96/116 (82.8)	1.6 (1.4, 2.6)	5.1	0.40 (0.29, 0.54) p<0.001

CI = confidence interval; *n* = number of participants reporting data; *N* = total participants in group

Source: Table 18, p61, Table 19, p62, Table 22, p65, Table 23, p66 of the submission.

- 6.11 In a post hoc comparison of ceritinib with the pemetrexed subgroup, the median PFS measured by BIRC favoured ceritinib by approximately ■ months, although the HR was not statistically significantly different from 1 (i.e. no effect) (Table 4 below).

^a Booth, C. M. and E. A. Eisenhauer (2012). "Progression-free survival: meaningful or simply measurable?" J Clin Oncol 30(10): 1030-1033. Cheema, P. and R. Burkes (2013). "Overall survival should be the primary endpoint in clinical trials for advanced non-small cell lung cancer." Current Oncology 20(2): 150-160.

Table 4 Results of progression free survival (BIRC and Investigator) for the pemetrexed subgroup in ASCEND-5

	Ceritinib		Pemetrexed		Difference in median months to event	Hazard ratio (95% CI)
	n/N with event (%)	Median months to event (95% CI)	n/N with event (%)	Median months to event (95% CI)		
BIRC	83/115 (72.2)	5.4 (4.1, 6.9)	██████████ (██████████)	██████████ (██████████, ██████████) ^a	██████████ (██████████, ██████████) ^b	██████████ (██████████, ██████████)
Investigator	83/115 (72.2)	6.7 (4.4, 7.9)	Not reported	██████████ (██████████, ██████████)	██████████	██████████ (██████████, ██████████)

CI = confidence interval; n = number of participants reporting data; N = total participants in group

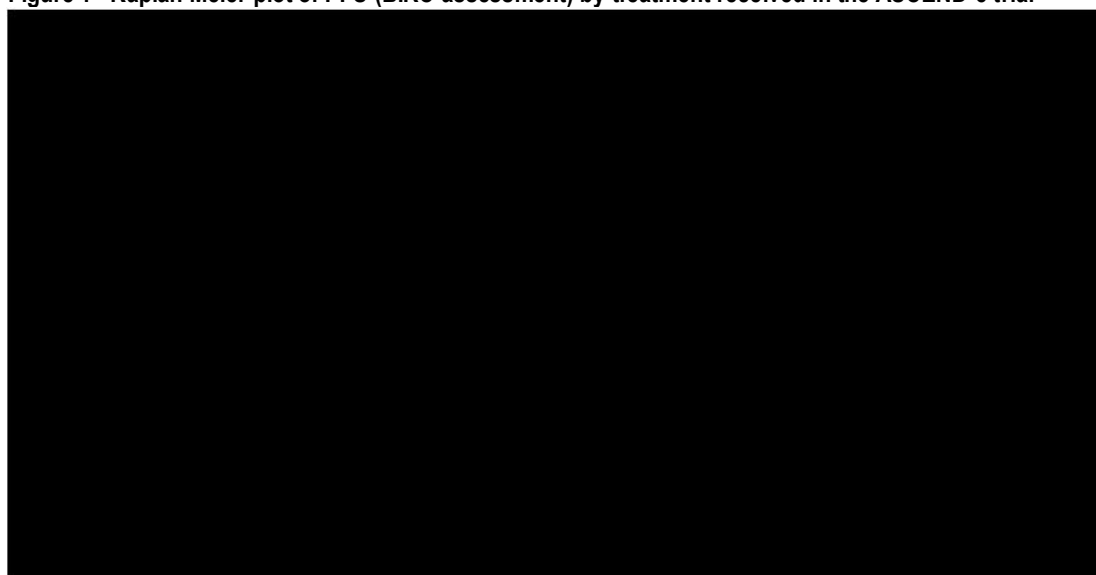
^aNote that the median time to event presented in the submission is slightly inconsistent with that presented in the FAR (2.9 months [95% CI 1.5, 5.1]). The submission references have not been provided (Post-text Supplement Figure 6-1; Figure 14.2-1.2a).

^bThe 95% confidence interval for the difference in medians has been calculated using the standard method for a difference between two statistically independent quantities assuming approximately normal distribution. It is not clear what approach has been used to estimate confidence intervals or whether an assumption of a normal distribution for this parameter is appropriate.

Source: Table 30, p71 of the submission and Table 14.2-1.1a of the First Available Results (FAR).

- 6.12 The Kaplan-Meier plots of PFS (BIRC assessment) by treatment are presented below.

Figure 1 Kaplan-Meier plot of PFS (BIRC assessment) by treatment received in the ASCEND-5 trial



BIRC = blinded independent review committee; CI = confidence interval;

Source: Figure 14.2-1.1a, p306 of the First Available Results.

- 6.13 The non-inferiority margin used in the submission for the HR (1.23) was not pre-specified. However, this non-inferiority margin is consistent with the ESC comments in the March 2015 public summary document for nintedanib for NSCLC (paragraph 6.9-6.11), which noted a HR of 1.21 to 1.25. The evaluation noted that that non-inferiority was tested for both PFS and OS for nintedanib and a non-inferiority margin for PFS is meaningful only when there is an accepted relationship between PFS and OS.

- 6.14 The ESC considered that based on the data presented in the submission, it was not clear whether a conclusion of non-inferiority for PFS would translate to the same conclusion for OS or quality of life.
- 6.15 The ESC also noted that the subgroup analysis was not pre-specified, and the allocation to pemetrexed or docetaxel in the control arm was not stratified. Therefore, the ESC considered that there is potential for imbalances in unreported prognostic factors and treatment effect modifiers between the treatment groups, resulting in potential bias.
- 6.16 There was no difference between ceritinib and chemotherapy arms in OS (full analysis set, HR 1.00 [95% CI 0.67, 1.49]). The evaluation noted that a HR may not be appropriate given there appears to be a crossing of the survival curves and a violation of the proportional hazards assumption. Nearly 65% of patients treated with chemotherapy switched to ceritinib on progression.
- 6.17 There was a substantial difference in median time to symptom deterioration based on the LCSS composite endpoint (pain, cough, shortness of breath) favouring the ceritinib arm (18 months vs 4.4 months), and a similar finding for the composite endpoint for EORTC QLQ-LC13 (pain, dyspnea and coughing) (11.1 months vs 2.1 months).
- 6.18 There was a statistically significant difference in EQ-5D score (scale of 0-1) favouring ceritinib over chemotherapy (0.08 [0.04, 0.13]). EQ-5D results were not presented for the pemetrexed subgroup.
- 6.19 A phase III randomised study of ceritinib in the first-line setting (versus chemotherapy) is currently underway with results expected in 2018 (ASCEND-4). A matching adjusted indirect comparison (MAIC) has been published that compared individual patient data from two single arm studies of ceritinib (ASCEND-1 and ASCEND-3) with the published data from three crizotinib trials (PROFILE 1001, 1005 and 1007)^b. The results for both pre-matching and post-matching analyses suggest that ceritinib may be superior in efficacy to crizotinib. Median PFS was 13.8 months in the ceritinib patients compared with 8.3 in the crizotinib patients (HR 0.52, 95% CI 0.44, 0.62). Further, OS was significantly longer (HR 0.59, 95% CI 0.46, 0.75) with ceritinib. However, there was no significant difference in overall response rate between ceritinib and crizotinib.

Comparative harms

- 6.20 Grade 3 and 4 adverse events (AEs) were more common in the ceritinib arm compared with patients receiving pemetrexed (■■■■% vs ■■■%). Similar numbers discontinued due to adverse events. Two on-treatment deaths were classified as caused by an AE, both in the ceritinib arm, but were not considered related to study treatment by investigator assessment. Table 5 below summarises the safety data from the ASCEND-5 trial.

^b Tan DSW, Araujo A, Zhang J, Signorovitch JE, Zhou ZY, Cai X, et al. Comparative efficacy of ceritinib and crizotinib in previously treated crizotinib-naïve anaplastic lymphoma kinase-positive (ALK+) advanced or metastatic non-small cell lung cancer (NSCLC): An adjusted indirect comparison. *Journal of Clinical Oncology* 2015;33(15).

Table 5 Summary of aggregate AE categories in ASCEND-5

	Ceritinib N=115 n (%)		Pemetrexed N=█ n (%)		Docetaxel N=73 n (%)	
	All grades	Grades 3/4	All grades	Grades 3/4	All grades	Grades 3/4
Any AE	115 (100)	89 (77.4)	█ (█)	█ (█)	72 (98.6)	54 (74)
Any AE resulting in discontinuation	18 (15.7)	15 (13)	█ (█)	█ (█)	7 (9.6)	5 (6.8)
On treatment death	15 (13.0)		█ (█)		3 (4.1)	
Any AE resulting in death	2 (1.7)		█ (█)		0 (0)	
AEs suspected to be drug-related	110 (95.7)	60 (52.2)	█ (█)	█ (█)	58 (79.5)	33 (45.2)

AE = adverse event

Source: Table 32, pp75-76 of the submission and Table 5-1, pp41-42 of the First Available Results (FAR) Primary analysis.

- 6.21 Ceritinib patients experienced a higher rate of gastrointestinal, cardiac and liver enzyme related AEs. The submission stated that this was not unexpected, and is consistent with the findings of other trials of ceritinib on which the registration was based. These findings led to the inclusion of a boxed warning in the approved Product Information. The boxed warning identifies the following serious adverse events and recommends close monitoring and early dose reduction: QT interval prolongation; interstitial lung disease/pneumonitis; hepatotoxicity; gastrointestinal toxicity. In addition, the boxed warning states that ceritinib has not been studied in patients with moderate and severe hepatic impairment, must be taken while fasting and should only be prescribed and supervised by a qualified physician experienced in the use of anticancer agents.
- 6.22 Patients receiving ceritinib were significantly more likely to experience a liver enzyme related Grade 3 or 4 AE than patients receiving pemetrexed. Grade 3 or 4 anaemia was more common in the pemetrexed arm. The ESC noted that the most common Grade 3 or 4 AEs were elevated liver enzymes, suggesting liver toxicity, increased incidence of vomiting and nausea and prolonged QT interval on electrocardiograph indicating an increased risk of cardiac arrhythmia.
- 6.23 The evaluation noted that the analysis of safety, which is reported for the on-treatment period, may have been confounded by the disparity of exposure to active therapy in each arm. Mean duration of exposure to ceritinib was █ weeks compared with █ weeks in the chemotherapy arm, or █ weeks in the pemetrexed subgroup. The duration of exposure to ceritinib was substantially longer than it was to pemetrexed, and the proportion of patients experiencing an adverse event would be expected to be higher.

Clinical claim

- 6.24 The submission described ceritinib as non-inferior in terms of efficacy and inferior in terms of safety to platinum doublet chemotherapy followed by pemetrexed, based on the subgroup analysis of ceritinib compared with pemetrexed in the ASCEND-5 trial.
- 6.25 The PBAC considered that the submission’s claim of at least non-inferiority for

efficacy and inferiority for safety was reasonable, and therefore that a cost-minimisation approach was appropriate.

Economic analysis

- 6.26 The submission presented a cost-minimisation analysis of ceritinib compared with the platinum chemotherapy followed by pemetrexed.
- 6.27 The equi-effective doses proposed in the submission were assumed on the basis that treatment duration with ceritinib and with platinum chemotherapy followed by pemetrexed would be the same, and the monthly cost of ceritinib was equal to the average monthly cost of chemotherapy followed by pemetrexed. The ESC did not consider this assumption reasonable, given the substantially longer treatment duration with ceritinib than with pemetrexed monotherapy as observed in ASCEND-5. Mean treatment duration with ceritinib in ASCEND-5 (■■■ months) remains longer than the assumed treatment duration of platinum chemotherapy (■■■ months) followed by pemetrexed (■■■ months), neither of which were sourced from the ASCEND-5 study.
- 6.28 Platinum doublet chemotherapy was assumed to be given on average ■■■ cycles followed by ■■■ cycles of pemetrexed maintenance. Administration costs of chemotherapy, pemetrexed and the costs associated with managing AEs were also included. There were a number of concerns in the submission's approach:
- The dosing of carboplatin, cisplatin and pemetrexed are consistent with eviQ treatment protocols^c, however, dosing intensity of ceritinib (■■■% of the recommended dose) and pemetrexed (■■■% of the recommended dose), as observed in ASCEND-5, was included. The application of a differential dosing intensity for ceritinib and pemetrexed, as observed in 3rd or later line setting, resulted in a higher price for ceritinib.
 - The duration of treatment with platinum chemotherapy was based on opinion of a limited number of clinicians;
 - The duration of pemetrexed maintenance was based on Ciuleanu et al (2009) in which the median progression-free survival (4.3 months) was reported.
 - The average duration may have been underestimated using the median PFS as the proxy for mean treatment duration. Median duration of treatment with pemetrexed in ASCEND-5 was ■■■ weeks, which was substantially shorter than the mean duration of ■■■ weeks.
 - On the other hand, the average duration of treatment with pemetrexed may have been overestimated, compared with the mean duration of pemetrexed observed in ASCEND-5. The submission argued that patients in ASCEND-5 were more heavily pre-treated than in the proposed PBS setting. If this is the case, the dosing intensity of ceritinib and pemetrexed would also be an inappropriate basis for the cost analysis.
 - The likely overestimate of the duration of pemetrexed was also due to the fact that Ciuleanu et al (2009) is a study of switch maintenance with pemetrexed versus placebo in the first-line setting. Patients are likely to achieve a longer duration of PFS, and thus longer duration of treatment, in the first-line setting than the proposed second- or later-line setting.

^c Cancer institute NSW, <https://www.eviq.org.au/>.

6.29 The submission estimated the monthly cost of the comparator by adding all of the costs of each treatment regimen (chemotherapy followed by pemetrexed) and dividing it by the average number of months of treatment. The submission’s approach to estimating an average monthly cost was inappropriate, since the cost of the comparator throughout the duration of the treatment is not constant: the cost of chemotherapy should only be applied in the first [redacted] cycles and the cost of pemetrexed in the second stage (next [redacted] cycles). The ratio of duration of chemotherapy to pemetrexed is important in this calculation, given the substantial difference in the cost of pemetrexed treatment and that of the platinum chemotherapy. The greater the proportion of overall treatment duration is applied to pemetrexed, the higher the average “per month” cost would be.

6.30 The submission’s approach to estimating the price of ceritinib is summarised below.

Table 6 The approach to estimating the average monthly cost of platinum chemotherapy followed by pemetrexed maintenance and the price of ceritinib

	Ceritinib	Chemo + Pemetrexed ^a	
		Chemo	Pemetrexed
Dose		Carboplatin AUC 5 Gem 1000 mg/m ² or Cisplatin 80 mg/m ² Gem 1250 mg/m ²	500 mg/m ²
The number of cycles ^b		[redacted] cycles	[redacted] cycles
Average number of months		[redacted] cycles x [redacted] days/ [redacted] days)	
Cost of regimen ^c		\$ [redacted] ^d	\$ [redacted] ^d
Average monthly cost		\$ [redacted] ^d	\$ [redacted] ^d
Dose intensity of pemetrexed in ASCEND-5			% ^e
Average monthly cost adjusted by dose intensity		\$ [redacted] ^d	
Average monthly administration cost (for managing AEs and drug administration)	\$ [redacted]		\$ [redacted]
Incremental monthly administration cost		\$ [redacted]	
Monthly cost of ceritinib	(=\$ [redacted] ^d + \$ [redacted])		
Dose intensity of ceritinib in ASCEND-5	%		
Proposed monthly cost of ceritinib (adjusted by dose intensity)	\$ [redacted] ^d (\$ [redacted] / [redacted])		
Proposed dispensed price per month	\$ [redacted] (\$ [redacted] + average co-payment \$ [redacted]) ^{d,f}		
Proposed ex-manufacturer price	\$ [redacted] ^{d,g}		

Chemo = chemotherapy; Gem = gemcitabine; AUC = area under the curve; AE = adverse event.

^a The body surface area was assumed to be 1.79m². The analysis is not sensitive to the cost of chemotherapy.

^b The number of cycles for chemotherapy was estimated by expert opinion. The number of cycles for pemetrexed was based on Ciuleanu et al (2009)

^c Weighted by 80% of patients receiving carboplatin and 20% cisplatin, based on expert opinion; 30% in public setting and 70% in private setting, based on PBS script data for pemetrexed.

^d The cost of regimen has been updated during the evaluation using the Efficient Funding for Chemotherapy fees as at 01/08/2016 and including \$20 more preparation fees for TGA licensed compounders.

^e The submission’s approach to including dose intensity is inappropriate. The dose intensity of [redacted]% observed from ASCEND-5 was only relevant to pemetrexed monotherapy, not chemotherapy regimen. If dose intensity is to be applied, it should be factored prior to the addition of dispensing fees, as these do not necessarily change relative to dose dispensed.

^f The average co-payment of \$23.52 was calculated using the distribution of crizotinib scripts across beneficiary types.

^g The ex-manufacturer price removes the wholesale mark-up (\$69.94), Administrative, Handling and Infrastructure (AHI) fee

(\$70.92) and ready-prepared dispensing fee (\$7.02) - <https://www.humanservices.gov.au/health-professionals/enablers/pricing-pharmaceutical-benefits-scheme-medicine#a6>

Source: Compiled during the evaluation

6.31 The evaluation noted that there is potential for the cost of a treatment course with ceritinib to be greater than the cost of a course of chemotherapy followed by pemetrexed maintenance. As observed in ASCEND-5, treatment with ceritinib was considerably longer than the treatment with pemetrexed monotherapy. The treatment with ceritinib in ASCEND-5 is also considerably longer than the treatment duration for platinum chemotherapy and pemetrexed maintenance assumed in the submission. The PSCR (p4-5) contended that a longer PFS (■■■■ months) was included in the cost analysis compared to ASCEND-5 assuming that Australian patients will be less heavily pre-treated. The ESC noted that the submission (and PSCR) quoted the median PFS for ceritinib (5.4 months) rather than mean, which was inappropriate for an analysis of costs. The ESC maintained that the submission's assumption of equivalent treatment duration remained a key issue in the cost-minimisation.

6.32 During the evaluation, a trial-based cost-minimisation analysis was performed, as follows:

Table 7 Trial-based cost-minimisation analysis

STEP	Description	Data	Note
1	Mean duration of therapy with pemetrexed (months)	■■■	First Available Results Table 14.3-1.1, p260
2	Mean duration of therapy with ceritinib (months)	■■■	First Available Results Table 14.3-1.1, p260
3	Cost of pemetrexed per cycle	\$■■■■■	(minus average co-pay of \$23.51)
4	Cost of pemetrexed per month	\$■■■■■	=■■■■■
5	Cost of pemetrexed at ■■■% RDI	\$■■■■■	=■■■■■%
6	Total cost of pemetrexed	\$■■■■■	=■■■■■
7	Monthly administration cost for pemetrexed	\$■■■■■	Infusion costs, clinician attendances, baseline and repeat bloods, metoclopramide, vitamin B12
8	Single per/course items for pemetrexed	\$■■■■■	2 x Dexamethasone, folic acid
9	Total administration cost for pemetrexed	\$■■■■■	=■■■■■
10	Monthly administration cost for ceritinib	\$■■■■■	Clinician attendances, baseline and repeat bloods, metoclopramide or prochlorperazine and loperamide
11	Single per/course items for ceritinib	\$■■■■■	ECG
12	Total administration cost for ceritinib	\$■■■■■	=■■■■■
13	Total cost of ceritinib at 80.3% RDI	\$■■■■■	=■■■■■
14	Total cost of ceritinib at 100%	\$■■■■■	=■■■■■%
15	Total monthly cost of ceritinib	\$■■■■■	=■■■■■ (minus average co-pay of \$■■■■■)

ECG = electrocardiography; RDI = relative dose intensity.

Source: generated during the evaluation.

Drug cost/patient/course: \$■■■■■

6.33 The average cost of ceritinib per patient per course was calculated during the evaluation to be \$■■■■■, based on the mean duration of therapy of ceritinib in

ASCEND-5 (■■■■ months), and the proposed price minus the average patient co-payment (\$■■■■, derived using trial based cost-minimisation proposed during evaluation).

- 6.34 The average cost per patient per course cannot be estimated for the comparator as no evidence is provided for the duration of platinum-based chemotherapy followed by pemetrexed. Based on the current price of pemetrexed per cycle (\$■■■■ for 500mg/m² for a patient with a body surface area of 1.79m², minus the average patient co-payment, and dispensed in the public setting), given for the average duration as observed in ASCEND-5 (■■■■ months or ■■■■ cycles), the average drug cost per patient for pemetrexed monotherapy is \$■■■■. The submission assumed that, on average, patients will take ■■■% of the recommended dose (500 mg/m²), and therefore the average cost per month will reduce to \$■■■■, and per course to \$■■■■.
- 6.35 The evaluation noted that these calculations do not incorporate the costs of infusions, premedications, professional attendances and treatments for adverse events. However, these costs are minor compared to the costs of ceritinib and pemetrexed.

Estimated PBS usage & financial implications

- 6.36 This submission was not considered by DUSC. The submission took an epidemiological approach to estimate the number of patients with *ALK*-positive, locally advanced or metastatic NSCLC. The submission derived the number of patients who would receive ceritinib using the following methodology:
- the estimated Australian population;
 - incidence of patients with non-squamous NSCLC (0.0241%);
 - proportion of patients with non-squamous NSCLC who are *ALK* positive (4.5%);
 - proportion of these patients who are diagnosed with advanced or metastatic disease (80%);
 - proportion of these eligible patients who would receive crizotinib (90%);
 - proportion of patients who would receive subsequent therapy following crizotinib (90%).
- 6.37 Using this method, the submission estimated that less than 10,000 patients would receive ceritinib in Year 5, with a net cost to the PBS of less than \$10 million at Year 5.

Table 8 Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Scripts ^a					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS					
Net cost to MBS					
Net cost to State and Territory governments					
Estimated total net cost					
Overall net cost to Australian governments					

^a Assuming █ scripts per patient (█ months x 80.3% relative dose intensity) as estimated by the submission.

Note: *Italicised numbers were respecified during the evaluation by changing the duration of treatment with ceritinib to █ months and of pemetrexed to █ months (█ cycles), and removing the costs associated with platinum-based chemotherapy (for which no evidence has been provided). All other costs (that are unrelated to platinum-based chemotherapy) used in the submission were retained.*

Source: Table 75, p128; Table 83, p135; Table 86, p137; Table 88, p138; and, Table 89, p138 of the submission. Costs for PBS and overall costs differ slightly from the submissions estimates as chemotherapy prices and dispensing fees were updated during the evaluation.

Quality Use of Medicines

- 6.38 The PBAC noted that ceritinib has drug-drug and drug-food interactions that have significant effect on its exposure, which might be difficult to manage in practice.
- 6.39 Further, the PBAC noted that the ASCEND-5 trial excluded patients with concurrent use of medications that are strong inducers of CYP3A4/5, or with a low therapeutic index and are metabolised by CYP3A4/5 or CYP2C9.

Financial Management – Risk Sharing Arrangements

- 6.40 The submission sought a Special Pricing Arrangement for ceritinib.

For more details on PBAC’s view, see section 7 “PBAC Outcome”.

7 PBAC Outcome

- 7.1 The PBAC recommended an Authority Required General Schedule listing of ceritinib for the treatment of *ALK*-positive NSCLC. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of ceritinib would be acceptable if it were cost-minimised against platinum chemotherapy followed by pemetrexed maintenance therapy.
- 7.2 In making this recommendation, the PBAC noted the relatively small population size (less than 10,000 patients/year) with *ALK*-positive NSCLC; the high clinical need for effective treatments for patients with this condition; and the likelihood that access to ceritinib would significantly improve quality of life in *ALK*-positive NSCLC patients

compared to chemotherapy. The PBAC considered that the submission's claim of at least non-inferiority for efficacy and inferiority for safety against platinum chemotherapy followed by pemetrexed maintenance therapy was reasonable, and therefore that a cost-minimisation approach was appropriate.

- 7.3 The PBAC noted the arguments presented in the sponsor's Pre-PBAC response (p3) in support of the submission's approach to the cost-minimisation calculation, but considered that the price derived using the trial-based cost-minimisation analysis conducted during the evaluation provided the most appropriate approach for calculating the price of ceritinib.
- 7.4 The PBAC noted that, in the post hoc analysis presented in the submission, the median PFS measured by BIRC favoured ceritinib by approximately ■■ months, although the HR was not statistically significant. The PBAC also noted that the results of this analysis were potentially confounded by the fact that a considerable proportion of patients (■■%) in the pemetrexed subgroup had been previously treated with pemetrexed. Further, the PBAC considered that no meaningful conclusions could be drawn regarding the effect of ceritinib on survival because nearly 65% of patients treated with chemotherapy switched to ceritinib on progression. However, despite these inherent drawbacks in the ASCEND-5 trial, the PBAC considered that ceritinib treatment resulted in clinically meaningful difference to a patient's quality of life, as evidenced by the improvement in lung cancer symptoms and health status (EQ-5D) from the trial, and the consumer comments received for this submission.
- 7.5 The PBAC noted that, while the submission's proposed PBS restriction positioned ceritinib after crizotinib, the evidence presented in the submission was in a different setting. The PBAC recalled it had previously recommended crizotinib as a first-line therapy for this condition, also largely on the basis of data from its use in a different setting (crizotinib Public Summary Document, November 2014 PBAC meeting). The PBAC therefore considered that allowing ceritinib treatment in any line of therapy was appropriate.
- 7.6 The PBAC noted that the financial estimates would need to be revised in light of its recommendation for the PBS listing of ceritinib for *ALK*-positive NSCLC without restricting the line of therapy. The PBAC considered that the revised estimates should also account for patients in the sponsor's compassionate use program, who may be eligible to receive ceritinib via a grandfathering arrangement.
- 7.7 The PBAC advised that ceritinib was not suitable for prescribing by nurse practitioners.
- 7.8 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

Public Summary Document – November 2016 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty Units	No. of Rpts	Proprietary Name and Manufacturer	
CERITINIB ceritinib 150 mg capsule, 50	150	1	Zykadia	Novartis Pharmaceuticals Australia Pty Ltd

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 (NSCLC)
PBS Indication:	stage IIIB (locally advanced) or stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Initial treatment
Restriction Level / Method:	<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
Clinical criteria:	The treatment must be as monotherapy AND The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC AND Patient must have a WHO performance status of 2 or less.
Population Criteria	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.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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

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Treatment phase:	Continuing treatment
Restriction Level / Method:	<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
Clinical criteria:	The treatment must be as monotherapy AND Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have progressive disease
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty Units	No. of Rpts	Proprietary Name and Manufacturer
<i>CERITINIB</i> ceritinib 150 mg capsule, 50	150	1	<i>Novartis Pharmaceuticals Australia Pty Ltd</i> Zykadia

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 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

Clinical criteria:	<p>Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to 1 February 2017 AND The treatment must be as monotherapy AND The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC AND Patient must have a WHO performance status of 2 or less AND Patient must not have progressive disease.</p>
Population criteria	<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>
Prescriber Instructions	<p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

9 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.

10 Sponsor's Comment

The sponsor had no comment.