5.01 ALECTINIB, Capsule 150 mg, Alecensa®, Roche Products Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 85, Authority Required listing for alectinib for the treatment of patients locally advanced (Stage IIIB) or metastatic (Stage IV) anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC), who have disease progression following treatment with a prior ALK inhibitor.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with ALK-positive locally advanced (Stage IIIB) or metastatic (Stage IV) non-squamous or NOS NSCLC, who have disease progression following treatment with a prior ALK inhibitor and a WHO performance status of 2 or less.
Intervention	Alectinib 600 mg (4 x 150 mg capsules) twice daily until progression.
Comparator	Ceritinib 750 mg (5 x 150 mg capsules) daily until progression.
Outcomes	Objective response rate (ORR) Duration of response (DOR) Progression-free survival (PFS) Overall survival (OS) CNS outcomes (including CNS objective response rate and CNS duration of response) Quality of life (QoL) Treatment-related adverse events
Clinical claim	In patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on an ALK inhibitor, represented by crizotinib, the submission claimed that alectinib is assumed to be superior to the main comparator ceritinib with respect to key systemic efficacy (ORR, DOR, PFS and OS) and CNS outcomes. The submission also claimed that alectinib has demonstrated a superior tolerability profile over ceritinib, with lower frequency and severity of key gastrointestinal (GI) events, specifically nausea and diarrhoea (including Grade 3-4 severity), likely to result in lower rates of GI toxicity-related hospitalisation, dose interruption, dose reduction, or drug discontinuation and a higher QoL. Acknowledging the limitations of superiority claims based on phase II single-arm comparisons, the submission presented a non-inferiority claim.

ALK = anaplastic lymphoma kinase; CNS = central nervous system; DOR = duration of response; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; WHO = World Health Organisation.
Source: Table 1.2, p7 Section 1 of the submission.

2 Requested listing

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 Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ALECTINIB Alectinib 150 mg capsule, 224	1	1	$[redacted] (published)	Alecensa Roche Products Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐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:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐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, AND ~~Patient must have disease progression, following treatment with a prior ALK inhibitor~~ *The condition must have progressed following treatment with a prior ALK inhibitor*; OR *Patient must have developed intolerance to a prior ALK inhibitor of a severity necessitating permanent treatment withdrawal*
Population criteria:	Patient must have prior evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as ≥ 15% positive cells by fluorescence in situ hybridisation (FISH) testing~~, previously performed at the time of initial biopsy for determination of ALK gene re-arrangement status for access to an initial ALK inhibitor.~~
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	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ALECTINIB Alectinib 150 mg capsule, 224	1	1	$[redacted] (published)	Alecensa Roche Products Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐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:	Continuing treatment
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Clinical criteria:	The treatment must be as monotherapy, AND Patient must have previously been issued with 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.*

2.1 In comparison to the TGA indication, the requested PBS listing:

- Did not include patients who were intolerant to crizotinib; and
- Allowed for use following progression on any ALK inhibitor, rather than specifying crizotinib.

2.2 No evidence was provided to support the use of alectinib subsequent to progression on any ALK inhibitor other than crizotinib.

2.3 The proposed listing did not specify the ALK inhibitor on which patients must have progressed in order to be eligible for alectinib. The proposed listing was, therefore, broader than the TGA indication, which specified that patients must have progressed on (or be intolerant to) crizotinib. The Pre-Sub-Committee-Response (PSCR) (p1) noted that the proposed PBS restrictions did not represent the final PBS listings recommended by the PBAC for both crizotinib and ceritinib, as both agents were recommended "in any line of therapy" by the PBAC (paragraph 7.7, crizotinib Public Summary Document (PSD), Nov 2014; paragraph 7.5, ceritinib PSD, Nov 2016), despite the TGA-approved use of ceritinib being restricted to second-line or later.

2.4 The submission was based on a cost-minimisation analysis of alectinib compared with ceritinib.

2.5 The recommended dose of alectinib is 600 mg (four 150 mg capsules) given orally, twice daily with food (total daily dose of 1,200 mg). Treatment should be continued until disease progression or unacceptable toxicity.

2.6 The submission acknowledged that special pricing arrangements apply to ceritinib. The submission stated that it was lodged on the basis of an in-principle agreement that the effective price for alectinib would be no higher than the cost-minimised effective price for the nominated comparator, ceritinib, on a cost per day of treatment basis, for patients with ALK-positive NSCLC who have progressed on a prior ALK inhibitor. The Pre-PBAC response (p.1) requested that, in the event of a recommendation to list alectinib without reference to any line of therapy, crizotinib

also be included as a comparator, and thus (p.3) the price of alectinib should also reflect the price of crizotinib.

For more detail on PBAC's view, see section 7 "PBAC outcome."

3 Background

3.1 Alectinib was recommended for registration by the TGA's Advisory Committee for Medicines on 2 February 2017, and was listed on the Australian Register of Therapeutic Goods on 14 March 2017, for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on, or are intolerant to, crizotinib.

3.2 The ESC noted that the Product Information (PI) for alectinib had a note in its indication section stating that "This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established."

3.3 This is the first submission of alectinib to the PBAC.

3.4 A similar submission for ceritinib was considered at the November 2016 PBAC meeting. The submission requested listing of ceritinib for the treatment of adult patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on a prior ALK inhibitor. The submission was based on a randomised controlled trial comparing ceritinib to chemotherapy in patients with ALK-positive NSCLC who had previously been treated with chemotherapy and crizotinib (ASCEND-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. The PBAC therefore considered that allowing ceritinib treatment in any line of therapy was appropriate (paragraph 7.5, 5.03 Ceritinib PSD, November 2016 PBAC Meeting).

4 Population and disease

4.1 ALK rearrangements are found in approximately 3-5% of cases of advanced NSCLC and are a distinct molecular subtype of lung cancer. Brain metastases are common in patients with ALK-positive metastatic NSCLC. Central nervous system (CNS) metastases are associated with a reduction in quality of life and reduced life expectancy compared with other metastatic sites, and treatments required for CNS disease control (corticosteroids, surgery, and radiation) are associated with considerable morbidity.

4.2 Alectinib is a selective *ALK* tyrosine kinase inhibitor which also has anti-*RET* (rearranged during transfection) activity. Alectinib inhibits ALK tyrosine kinase activity, leading to a blockage of downstream signalling pathways, and inhibits

proliferation of cancer cells harbouring EML4-ALK (echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase) fusion proteins.

4.3 The submission requested that alectinib be listed for the treatment of patients with locally advanced or metastatic ALK-positive NSCLC, who have disease progression following treatment with a prior ALK inhibitor (i.e. second- or later-line therapy). The submission stated that it was awaiting results from ALEX, a randomised controlled trial comparing alectinib and crizotinib in treatment-naïve patients with ALK-positive NSCLC, prior to lodging a submission for use of alectinib for previously untreated ALK-positive NSCLC.

4.4 The proposed positioning of alectinib in the treatment of ALK-positive locally advanced or metastatic NSCLC was as an alternative second-line treatment option in patients who have progressed following treatment with a prior ALK inhibitor. This was not consistent with the clinical evidence presented in the submission, in which 77% of patients in the alectinib studies had previously received chemotherapy in addition to crizotinib.

4.5 The ESC noted that the clinical place of alectinib was uncertain as there was limited clinical evidence currently available comparing alectinib with other ALK inhibitors.

5 Comparator

5.1 The submission nominated ceritinib as the main comparator. Ceritinib is the appropriate comparator for the use of alectinib subsequent to progression in patients receiving crizotinib as the initial ALK inhibitor therapy. The evidence presented in the submission is consistent with this use, although the patients in the studies represented a more heavily pre-treated population than anticipated in Australian clinical practice.

5.2 Alectinib may also be used following progression on either first- or later-line ceritinib. The submission did not nominate a separate comparator for this use. As there is no evidence to support the use of crizotinib in patients who have progressed on a prior ALK inhibitor, if alectinib is used in patients who have progressed on ceritinib, it would most likely replace chemotherapy (or displace it to a later line of treatment).

5.3 If alectinib is used following progression on first-line crizotinib, the current restriction of ceritinib would still allow for it to be used for treatment after progression on alectinib (i.e. third line). As such, the PBS listing of alectinib would potentially displace, rather than replace, ceritinib to a later line of therapy.

- The submission stated that the sponsor's Advisory Board, consisting of nine Australian medical oncologists, confirmed that chemotherapy would be preferentially used as a third-line treatment, as opposed to sequential use of three ALK inhibitors.

- The ESC noted that the proposed listing for alectinib does not restrict third- or later-line access to alectinib, and therefore if recommended for listing, alectinib could be used to replace chemotherapy in later lines of therapy.
- The ESC noted that no clinical evidence comparing alectinib to chemotherapy was provided in the submission.
- The ESC recalled that ceritinib was recommended by the PBAC on a cost-minimisation basis against platinum chemotherapy followed by pemetrexed maintenance therapy (ceritinib PSD, Nov 2016).

For more detail 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 (173) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with alectinib, emphasising fewer side effects, and an effect on brain metastases.

6.3 The Lung Foundation considered that alectinib represents an important second-line treatment option for ALK-positive lung cancer patients who have progressed on first-line targeted treatment. The comment from Rare Cancers Australia noted that the PBS listing of alectinib would make a difference to patients by slowing disease progression, potentially allowing them time to access novel treatment in the future.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the alectinib submission, due to its high level of activity in pre-treated patients. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for alectinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with crizotinib.

Clinical trials

6.5 The submission was based on a naïve indirect comparison of two single-arm studies of alectinib (NP28761, N=87 and NP28673, N=138) and two single-arm studies of ceritinib (ASCEND-1, N=163 and ASCEND-2, N=140) in patients with locally advanced

[1] Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 26:1547-73, 2015

or metastatic ALK-positive NSCLC previously treated with crizotinib. Results based on unweighted pooled data from the two alectinib studies were also provided. ASCEND-1 included an ALK inhibitor naïve group (N=83), which was not included in the submission. The submission also presented a retrospective indirect comparison of alectinib data from NP28761 and NP28673 with a cohort of 'real world' patients treated with ceritinib (study MO39246).

6.6 The literature search identified two unpublished randomised controlled trials (RCTs) that would have allowed an indirect comparison of alectinib and ceritinib via a common chemotherapy arm (ALUR and ASCEND-5, respectively). The sponsor released a media statement on 3 April 2017[2], stating that the ALUR trial demonstrated that, compared to chemotherapy, alectinib significantly improved progression-free survival (PFS) in patients with ALK-positive advanced NSCLC who had progressed following treatment with one prior line of platinum-based chemotherapy and crizotinib. No further details were provided at the time.

6.7 The November 2016 submission for ceritinib was based on ASCEND-5, an open-label RCT comparing ceritinib (N=115) to chemotherapy (pemetrexed or docetaxel) (N=116) in patients with ALK-positive advanced NSCLC who had previously been treated with crizotinib and platinum-doublet chemotherapy. Preliminary effectiveness data from the ceritinib arm of the ASCEND-5 trial were presented, where available.

6.8 Details of the studies presented in the submission are provided in the table below.

[2] http://www.roche.com/media/store/releases/med-cor-2017-04-03.htm

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Alectinib single-arm studies		
NP28761	Clinical study report – NP28761/AF-002JG – A Phase I/II study of the ALK inhibitor CH5424802/RO5424802 in patients with ALK-rearranged non-small cell lung cancer previously treated with crizotinib. Report No. 1061912.	May 2015
	Shaw A, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: A single-group, multicentre, phase 2 trial.	Lancet Oncology 2016; 17 (2):234-42.
NP28673	Clinical study report – NP28673 - –n open-label, non-randomised, multicentre Phase I/II trial of RO5424802 given orally to non-small cell lung cancer patients who have ALK mutation and who have failed crizotinib treatment. Report No. 1060154.	May 2015
	Ou S, Ahn J, Govindan R, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small cell lung cancer: A phase II global study.	Journal of Clinical Oncology 2016; 34 (7):661-68.
NP28761/NP28673 Pooled data	Clinical study reports: EU safety update report for alectinib (RO5424802) Clinical overview addendum Summary of clinical efficacy Summary of clinical safety	July 2016
Ceritinib single-arm studies		
ASCEND-1	Kim DW, Mehr R, Tan, D, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial.	Lancet Oncology 2016; 17:452-63.
ASCEND-2	Crino L, Ahn MJ, De Marinis F, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non–small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2.	Journal of Clinical Oncology 2016; 34 (24):2866-73.
Supplementary study		
MO39246	Clinical study report - Comparative efficacy In ALK-positive non-small cell lung cancer patients following progression with crizotinib: a comparison of alectinib phase II data versus ceritinib real-world data.	February 2016

Source: Table 2.4, p10, Section 2 of the submission.

6.9 The key features of the single-arm studies are summarised in the table below.

Table 3: Key features of the evidence included in the submission– naive indirect comparison

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes
Alectinib					
NP28761	87	MC, SA, OL* Median 17.0 months	High	Failed crizotinib	ORR, PFS, OS
NP28673	138	MC, SA, OL* Median 21.3 months	High	Failed crizotinib	ORR, PFS, OS
Ceritinib					
ASCEND-1	163	MC, SA, OL* Median 11.1 months	High	Prior crizotinib	ORR, PFS, OS
ASCEND-2	140	MC, SA, OL* Median 11.3 months	High	Failed crizotinib Prior chemotherapy	ORR, PFS, OS
ASCEND-5** Ceritinib arm	115	MC, RCT, OL* Median 16.5 months	Low	Failed crizotinib Failed chemotherapy	ORR, PFS, OS

ALK = anaplastic lymphoma kinase; MC = multi-centre; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; SA = single arm.

* In all studies, response outcomes were assessed by both the investigator and a blinded independent review committee.

** ASCEND-5 was not included in the submission but was included in the evaluation where results were available. Only the ceritinib arm of the trial was relevant to the submission.

Source: compiled during the evaluation.

6.10 The submission stated that outcomes in all studies were assessed by both the investigator and a blinded independent review committee (IRC), and that the IRC in the alectinib studies did not have access to treatment arm information. It was not clear how blinding of the IRC was maintained given these were single-arm studies.

6.11 All four studies enrolled patients with locally advanced or metastatic ALK-positive NSCLC, with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. All patients had previously received crizotinib, although only 91% of patients in ASCEND-1 had progressed on prior ALK inhibitor therapy. ASCEND-2 also required patients to have received prior treatment with at least one platinum-based chemotherapy regimen. In all four studies, patients with CNS metastases were only eligible if they were asymptomatic and had stable CNS disease.

6.12 The ESC noted that study populations were heavily pre-treated. The majority of patients in both the alectinib and ceritinib studies had received prior chemotherapy in addition to crizotinib treatment (77% and 91%, respectively), and approximately 55% of patients in both sets of studies had received three or more lines of therapy. The PSCR (p5) claimed that subgroup analyses of PFS by prior chemotherapy presented in the submission showed that alectinib achieved similar PFS outcomes regardless of whether patients had prior chemotherapy or not.

6.13 In a naïve indirect comparison of single-arm studies, it is not possible to use the event rate in a common reference arm to assess and adjust for any imbalances in both observed and unobserved confounding factors that may exist, based on the assumption of a constant relative treatment effect across baseline risks. Furthermore, an unadjusted indirect comparison, in which the results of single-arm studies are compared as if they were from a single trial, does not take into account between study variation, and so the resulting confidence intervals will

underestimate the true extent of statistical uncertainty in the synthesised estimate of the comparative treatment effect.[3]

6.14 The comparison of efficacy outcomes between the two sets of studies was potentially confounded by differences between the study populations in terms of the proportion of patients who had only received one prior anti-neoplastic therapy ([redacted]% in the alectinib studies vs. 9% in the ceritinib studies), potentially favouring alectinib, and the proportion of Asian patients (19% vs. 33% in the alectinib and ceritinib studies, respectively), potentially favouring ceritinib[4].

6.15 There were insufficient comparable baseline characteristics reported across the studies to allow a full assessment of differences in factors that may affect the transitivity of the studies. In any comparison of single-arm studies, there is also considerable potential for confounding due to imbalances in unobserved prognostic factors or treatment effect modifiers across the studies, or undocumented differences in study conduct.

6.16 All four studies allowed treatment with the study drug to be continued beyond progression in patients who were still experiencing clinical benefit, as determined by the investigator. Details of the extent of use of the study drug beyond progression could only be located for ASCEND-1.

6.17 The study report for MO39246 reported that [redacted] ([redacted]%) patients in NP28761 and NP28673 received ceritinib in subsequent follow-up. Limited information was provided regarding anti-neoplastic therapies received after discontinuation of the study drug in the ceritinib studies, although no patients in ASCEND-1 received alectinib within 28 days of discontinuing ceritinib.

6.18 In NP28761 and NP28673, the primary efficacy outcome was the objective response rate (ORR) in the response evaluable (RE) population[5], as assessed by the IRC. On review of all radiographs, the IRC excluded 20/87 (23.0%) patients in NP28761 and 16/138 (11.6%) patients in NP28673 from the RE population, as they were not considered by the IRC to have measurable disease at baseline. In contrast, the analysis of ORR in the ceritinib studies (assessed by the IRC) was based on the full analysis set (FAS), which included all patients who received at least one 750 mg dose of ceritinib.

6.19 Comparing the ORR results in the IRC RE population from the alectinib studies with those in the FAS from the ceritinib studies, as presented in the submission, biased the comparison in favour of alectinib, as patients without measurable disease at baseline in the ceritinib studies were imputed as treatment failures, while they were excluded from the RE analysis in the alectinib studies. During the evaluation, the IRC assessed ORR results for alectinib were recalculated based on the FAS.

[3] Indirect Comparisons Working Group to the Pharmaceutical Benefits Advisory Committee. Report of the Indirect Comparisons Working Group to the Pharmaceutical Benefits Advisory Committee: assessing indirect comparisons. 2009.
[4] Asian ethnicity is a favourable prognostic factor for overall survival in NSCLC (Ou et al, *J Thorac Oncol* 2009; 4:1083-93).
[5] The RE population was defined as all patients with measurable disease at baseline who had a baseline tumour assessment and received at least one dose of alectinib.

6.20 The PSCR (p5) presented the investigator assessed PFS results for the open-label phase III ALUR trial comparing alectinib with chemotherapy in patients with ALK-positive locally advanced or metastatic NSCLC who had previously been treated with platinum-based chemotherapy and crizotinib. The PSCR (p5) presented an indirect comparison of alectinib versus ceritinib with platinum-based chemotherapy as a common reference, based on the outcome of investigator assessed PFS from the ALUR and ASCEND-5 trials, and claimed that alectinib significantly reduced the risk of progression relative to ceritinib. The PSCR claimed that the results were in favour of alectinib. The ESC did not consider these results as part of its deliberations on the effectiveness of alectinib as they had not been independently evaluated.

6.21 The ESC noted that the PSCR (p2) presented the preliminary results for the investigator assessed PFS from the ALEX trial comparing alectinib versus crizotinib in treatment-naïve patients with ALK-positive advanced NSCLC. These data were not considered in the ESC's deliberations as they had not been independently evaluated.

6.22 The pre-PBAC response (p1-2) claimed that data from the phase 3 ALUR study indicated that alectinib was superior to chemotherapy in terms of PFS. The pre-PBAC response further claimed that alectinib's safety and tolerability profile was consistent with the phase 2 trials, and that it was superior to chemotherapy in relation to comparative safety. The pre-PBAC response (p1) presented further results for the investigator assessed PFS and the OS (ITT) from the ALEX trial as well. However, these data were not considered in the PBAC's deliberations as they had not been independently evaluated.

Comparative effectiveness

6.23 Table 4 summarises the median PFS and median overall survival (OS) across the single-arm studies and the ceritinib arm of ASCEND-5.

Table 4: Median PFS and OS across the single-arm studies and the ceritinib arm of ASCEND-5 (FAS)

Outcome	Alectinib			Ceritinib		
	NP28761 N=87	NP28673 N=138	Unweighted pooled total N=225	ASCEND-1 N=163	ASCEND-2 N=140	ASCEND-5 N=115
Progression-free survival – IRC assessed						
Patients with event, n (%)	58 (66.7%)	98 (71.0%)	156 (69.3%)	NR	NR	NR
Median PFS, months (95% CI)	8.2 (6.3, 12.6)	8.9 (5.6, 12.8)	8.3 (7.0, 11.3)	7.0 (5.7, 8.7)	7.2 (5.4, 9.0)	5.4 (4.1, 6.9)
Overall survival						
Patients with event, n (%)	36 (41.4%)	60 (43.5%)	96 (42.7%)	63 (38.7%)	NR	NR
Median OS, months (95% CI)	22.7 (17.2, NE)	26.0 (21.5, NE)	26.0 (21.4, NE)	16.7 (14.8, NE)	14.9 (13.5, NE)	18.1 (13.4, 23.9)

CI = confidence interval; FAS = full analysis set; IRC = independent review committee; NE = not evaluable; NR = not reported; OS = overall survival; PFS = progression-free survival.
Source: Table 2.25 p46 and Table 2.49 p73 Section 2 of the submission; Kim et al (2016); Scagliotti et al (2016).

6.24 The submission stated that the time to event outcomes favoured alectinib, with a numerically longer median PFS, and a substantial and clinically meaningful difference in median OS for alectinib relative to ceritinib, with a numerical median OS difference of 9.3-11.1 months. The OS data for all studies were relatively immature, with only 39%-43% of patients across the studies having experienced an event. The

comparison of median OS was potentially confounded by differences in post-progression therapies between the studies.

6.25 The difference in the point estimate of median PFS (assessed by an IRC) between the pooled alectinib studies (8.3 months) and the ceritinib studies (5.4-7.2 months) ranged from 1.1–2.9 months. The submission did not establish the clinical importance of a difference in median PFS of this magnitude.

6.26 IRC assessed and investigator assessed ORRs from the single-arm studies are presented below.

Table 5: Results of objective response rate across the single-arm studies

	Alectinib		Ceritinib		
	NP28761	NP28673	ASCEND-1	ASCEND-2	ASCEND-5
IRC assessed (FAS)					
ORR, n/N (%) (95% CI)	[redacted]	[redacted]	75/163 (46.0%) (38.2%, 54.0%)	50/140 (35.7%) (27.8%, 44.2%)	45/115 (39.1%) (31.2%, 48.7%)
IRC assessed (RE/PP population)[a]					
ORR, n/N (%) (95% CI)	35/67 (52.2%) (39.7%, 64.6%)	62/122 (50.8%) (41.6%, 60.0%)	-	50/102 (49.0%) (39.0%, 59.1%)	-
Investigator assessed (FAS population)[b]					
ORR, n/N (%) (95% CI)	46/87 (52.9%) (41.95, 63.7%)	71/138 (51.4%) (42.8%, 60.0%)	92/163 (56.4%) (48.4%, 64.2%)	54/140 (38.6%) (30.5%, 47.2%)	49/115 (42.6%) (33.4%, 52.2%)
DOR, months Median (95%CI)	[redacted]	[redacted]	8.3 (6.8, 9.7)	9.7 (7.1, 11.1)	NR

CI = confidence interval; DOR = duration of response; FAS = full analysis set; IRC = independent review committee; NR = not reported; ORR = objective response rate; PP = per protocol; RE = response evaluable.

[a] IRC assessed RE population in NP28761 and NP28673, and IRC assessed PP population in ASCEND-2.

[b] The investigator RE population in the alectinib studies included all patients in the FAS (all treated patients).

Source: Table 2.22 p43, Table 2.24 p45, Table 2.30 p52 and Table 31 p52 Section 2 of the submission; Scagliotti et al (2016).

6.27 The pooled results for IRC assessed ORR based on the FAS were similar for both drugs ([redacted]% vs 41% for alectinib and ceritinib, respectively), as were the investigator assessed results ([redacted]% and 47% for alectinib and ceritinib, respectively). The investigator reported median duration of response was longer in the alectinib studies compared to the ceritinib studies.

6.28 Table 6 presents the results of the naïve indirect comparison of ORR.

Table 6: Summary of results of the naïve indirect comparison for objective response rate

	Trial ID	*n* with event/*N* (%)	Alectinib vs. ceritinib		
			Odds ratio (95% CI)	Relative risk (95% CI)	Risk difference (95% CI)
IRC assessed ORR (FAS)					
Alectinib studies	NP28761	[redacted]	[redacted]	[redacted]	[redacted]
	NP28673	[redacted]			
	Unweighted pooled total	[redacted]			
Ceritinib studies	Unweighted pooled study results	125/303 (41.3%)			
	ASCEND-1	75/163 (46.0%)			
	ASCEND-2	50/140 (35.7%)			
IRC assessed ORR (RE population in alectinib studies and FAS in ceritinib studies)[a]					
Alectinib studies RE population	Unweighted pooled total	[redacted]	[redacted]	[redacted]	[redacted]
Ceritinib studies FAS population	Unweighted pooled study results	125/303 (41.3%)			

CI = confidence interval; FAS = full analysis set; IRC = independent review committee; ORR = objective response rate; RE = response evaluable.
[a] As presented in the submission.
Figures in italics were calculated during the evaluation.
Source: Table 2.47, p71 and Table 2.48, p72 Section 2 of the submission.

6.29 The submission claimed that formal analyses conducted on pooled study ORR rates indicated that alectinib was superior to ceritinib with respect to ORR, as assessed by the IRC. The results of the analysis presented in the submission were biased in favour of alectinib, as the analysis compared results for alectinib in the RE population with those for ceritinib based on the FAS. The analyses based on the FAS for both sets of studies failed to demonstrate any difference in IRC assessed ORR between the two sets of studies.

6.30 The results for the main outcomes assessing CNS activity, CNS ORR and duration of CNS response, in patients with measurable CNS lesions at baseline, are presented below.

Table 7: Results of IRC assessed CNS objective response rate across the single-arm studies in patients with measurable CNS disease at baseline

Outcome	Alectinib			Ceritinib	
	NP28761[a]	NP28673[a]	Unweighted pooled total[a]	ASCEND-1[a, b]	ASCEND-2[c]
CORR, n/N (%) (95% CI)	12/16 (75.0%) (47.6%, 92.7%)	20/34 (58.8%) (40.7%, 75.4%)	32/50 (64.0%) (49.2%, 77.1%)	10/28 (35.7%) (18.6%, 55.9%)	13/33 (39.4%) (22.9%, 57.9%)
CR, n/N (%)	4/16 (25.0%)	7/34 (20.6%)	11/50 (22.0%)	0	1/33 (3.0%)
PR, n/N (%)	8/16 (50.0%)	13/34 (38.2%)	21/50 (42.0%)	10/28 (35.7%)	12/33 (36.4%)
CDOR, months Median (95%CI)	11.1 (5.8, NE)	11.1 (7.1, NE)	11.1 (7.6, NE)	11.1 (2.8, NE)	NR

CDOR = central nervous system duration of response; CI = confidence interval; CORR = central nervous system objective response rate; CR = complete response; DCR = disease control rate; IRC = independent review committee; NE = not evaluable; NR = not reported; PR = partial response.
[a] Based on patients with measurable CNS disease at baseline.
[b] Post hoc analysis.
[c] Based on patients with active target lesions at baseline.
Source: Table 2.51 p76 Section 2 of the submission.

Table 8: Summary of results of the naïve indirect comparison for IRC assessed CNS objective response rate

	Trial ID	n with event/N (%)	Alectinib vs. ceritinib		
			Odds ratio (95% CI)	Relative risk (95% CI)	Risk difference (95% CI)
Alectinib studies	NP28761	12/16 (75.0%)[a]	2.94 (1.35, 6.38)	1.70 (1.16, 2.49)	26.3% (8.3%, 44.3%)
	NP28673	20/34 (58.8%)[a]			
	Unweighted pooled total	32/50 (64.0%)[a]			
Ceritinib studies	Unweighted pooled study results	23/61 (37.7%)			
	ASCEND-1	10/28 (35.7%)[a, b]			
	ASCEND-2	13/33 (39.4%)[c]			

CI = confidence interval; CNS = central nervous system; ORR = objective response rate.
[a] Based on patients with measurable CNS disease at baseline.
[b] Post hoc analysis.
[c] Based on patients with active target lesions at baseline.
Source: Tables 2.51 and 2.52, p76 Section 2 of the submission.

6.31 The submission claimed that alectinib was superior to ceritinib in terms of CNS ORR, as determined by the IRC. The analyses in ASCEND-2 were based on patients with active CNS target lesions, while the analyses in the other studies included all patients with measurable CNS lesions. The extent and direction of any bias resulting from this difference in patient populations is not clear. Given the small sample sizes, and the fact that the indirectly derived confidence intervals do not reflect the true extent of statistical uncertainty in the synthesised estimate of the comparative treatment effect, the results of this analysis should be interpreted with caution. No difference in median duration of response was evident.

Comparative harms

6.32 The main safety outcomes across the single-arm studies are presented in Table 9.

Table 9: Summary of the results of the naïve indirect comparison of safety outcomes

	Alectinib			Ceritinib		Alectinib (pooled) vs. ceritinib (pooled)
	NP28761 N=87	NP28673 N=138	Unweighted pooled total N=253[a]	ASCEND-1 N=246[b]	ASCEND-2 N=140	Relative risk (95% CI)
Median duration of follow-up, months	17.0	21.3	-	11.1	11.3	
Any AE, n (%)						
Total	87 (100%)	137 (99.3%)	250 (98.8%)	246 (100%)	140 (100.0%)	0.99 (0.97, 1.00)
Drug-related	69 (79.3%)	104 (75.4%)	197 (77.9%)	238 (97%)	135 (96.4%)	0.81 (0.75, 0.86)
Grade 3-4 AEs, n (%)[c]						
Total	34 (39.1%)	50 (36.2%)	93 (36.8%)	200 (81.3%)	100 (71.4%)	0.47 (0.40, 0.56)
Drug-related	12 (13.8%)	16 (11.6%)	33 (13.0%)	125 (50.8%)	64 (45.7%)	0.27 (0.19, 0.37)
Serious AE, n (%)						
Total	15 (17.2%)	31 (22.5%)	55 (21.7%)	117 (48%)	57 (40.7%)	0.48 (0.37, 0.62)
Drug-related	3 (3.4%)	10 (7.2%)	15 (5.2%)	29 (12%)	24 (17.1%)	0.43 (0.25, 0.75)
Discontinuation due to AE, n (%)	2 (2.3%)	12 (8.7%)	15 (5.9%)	26 (11%)	11 (7.9%)	0.62 (0.35, 1.10)
Death due to AE, n (%)						
Total	2 (2.3%)	5 (3.6%)	7 (2.8%)	2 (0.8%)	0	5.34 (1.12, 25.5)
Drug-related	1 (1.1%)	1 (0.7%)	2 (0.8%)	2 (0.8%)	0	1.53 (0.22, 10.8)

AE = adverse event; CI = confidence interval.

[a] Pooled data includes patients from both Phase I and II of NP28761 (only patients who received 600 mg alectinib twice daily were included), and Phase II and a midazolam drug-drug interaction sub-study of NP28673.

[b] Information only available for combined ALK inhibitor naïve (N=83) and ALK inhibitor pre-treated (N=163) population.

[c] The number of Grade 3-4 AEs in the alectinib studies was calculated as the number of Grade 3-5 AEs minus the number of deaths due to AEs.

Source: p59, Table 2.35 p57, Table 2.53 p 77 and Table 2.54 p78 Section 2 of the submission; Kim et al (2016); Crino et al (2016).

6.33 The limitations of the naïve indirect comparison, discussed above in regard to the effectiveness outcomes, apply equally to the comparison of safety outcomes.

6.34 The submission stated that Grade ≥ 3 adverse events (AEs), both drug-related and all-cause, occurred significantly less frequently on alectinib treatment than ceritinib treatment. The proportion of patients experiencing at least one Grade 3-4 AE and serious AEs, both all cause and drug-related, was lower in the alectinib studies compared to the ceritinib studies.

6.35 There were more deaths due to AEs in the alectinib studies (7/253, 2.8%) compared to the ceritinib studies (2/386, 0.5%)[6], although only two of the seven deaths in the alectinib studies were considered by the investigator to be related to the study drug. The difference in the number of deaths due to AEs was not due to differences in follow-up between the studies, as six of the deaths in the alectinib studies had occurred prior to earlier data cut-off dates, when the median duration of follow up was less than 11 months in both studies. However, given the small sample sizes and

[6] The deaths in the alectinib studies were attributed to haemorrhage (2 patients), dyspnoea, endocarditis, intestinal perforation, pulmonary embolism, and unspecified (1 patient each). The two deaths in the ceritinib studies were due to interstitial lung disease, and multi-organ failure in the context of infection and ischaemic hepatitis.

the indirect nature of the comparison, the difference between the studies in terms of deaths due to AEs should be interpreted with caution.

6.36 The safety results suggested that ceritinib is associated with a higher incidence of Grade 3-4 diarrhoea, nausea and vomiting compared to alectinib. Myalgia and creatinine phosphokinase elevation were prominent AEs in the alectinib studies. [redacted] Cases of severe interstitial lung disease/pneumonitis have been reported with both drugs.

6.37 There are currently insufficient data to fully define the safety profile of alectinib, especially in terms of the less common AEs. The ESC agreed with this, noting that clinical data comparing alectinib to other ALK inhibitors were particularly limited, and considered that alectinib's safety profile would vary with its clinical place in therapy.

Benefits and harms

6.38 The naïve indirect comparison presented in the submission did not allow for a robust comparison of the benefits and harms of alectinib and ceritinib. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.39 The submission stated that the effectiveness and safety of alectinib is assumed to be superior to ceritinib. However, acknowledging the limitations of superiority claims based on single-arm studies, the submission presented a non-inferiority claim. The ESC considered that the clinical place of alectinib was likely to have a significant impact on its efficacy and safety profile, and therefore ambiguity about its clinical place in therapy hindered the assessment of the submission's claim of non-inferiority versus ceritinib.

6.40 The submission's statement regarding the assumption of superiority to ceritinib in terms of effectiveness was based on numerically higher ORRs, and numerically longer median PFS and median OS. The submission also claimed that, for patients with measurable CNS metastases at baseline, alectinib demonstrated higher CNS ORR, including complete responses. The ESC considered that the data presented in the submission was not sufficient to ascertain the magnitude of incremental benefit, if any, of alectinib versus ceritinib, in relation to CNS metastases.

6.41 Given the unadjusted indirect nature of the comparison, and the considerable risk of confounding and bias, it was not possible to make any reliable conclusions regarding the comparative effectiveness and safety of alectinib and ceritinib.

- The comparison of median OS was potentially confounded by differences in post-progression therapies between the studies.
- The ESC considered that the clinical importance of the observed difference in the point estimates of IRC assessed median PFS between the alectinib and ceritinib studies (1.1 – 2.9 months) was uncertain.

- The submission's claim in regard to the numerically higher ORR was based on a biased analysis, in which the results of the IRC assessed ORR in the RE population of the alectinib studies was compared with the IRC assessed ORR in the FAS of the ceritinib studies.
- The claim regarding the higher CNS ORR was based on a naïve indirect comparison of small subgroups which may have differed across the studies in terms of the type of CNS lesions on which the outcome was determined.
- There were more AEs resulting in death in the alectinib studies (7/253, 2.8%) compared to the ceritinib studies (2/386, 0.5%), although only 2 of the deaths in the alectinib studies were considered to be study drug-related. This difference should be interpreted with caution given the unadjusted indirect nature of comparison and the small sample sizes in the studies.

6.42 The submission acknowledged that the patients enrolled in the studies represented a more heavily pre-treated population than anticipated in Australian clinical practice. The PSCR (p3) argued that alectinib overall survival outcomes were not driven by differences in prior pre-treatments and noted that ceritinib real world overall survival outcomes[7] ([redacted] months) were relatively concordant with those in the Phase II studies ASCEND-1 (16.7 months) and ASCEND-2 (14.9 months). Despite this, the ESC considered that the alectinib study results may have limited applicability to the Australian clinical setting, given that patients on second- and third-line treatments generally have poorer outcomes compared with treatment-naïve patients.

6.43 The PBAC considered that it was difficult to draw meaningful conclusions regarding the extent of incremental benefit versus ceritinib, if any, on CNS response in patients with measurable CNS lesions, given the small sample sizes across both sets of studies and the indirect nature of the comparison. However, overall, the PBAC considered that the submission's claim of non-inferior comparative effectiveness against ceritinib was reasonable.

6.44 The PBAC considered that, based on the data presented in the submission, alectinib and ceritinib had different side effect profiles. The PBAC advised that, although currently available clinical data was insufficient to fully define the safety profile of alectinib, it was reasonable to conclude that it was non-inferior in terms of comparative safety, compared with ceritinib.

Economic analysis

6.45 The submission acknowledged that ceritinib is listed on the PBS under a Special Pricing Arrangement. The submission stated that a cost-minimisation analysis using the published price of ceritinib was presented with an in-principle agreement that the effective price for alectinib would be no higher than the cost-minimised effective price for ceritinib on the basis of the cost per day of treatment.

[7] Clinical study report - Comparative Efficacy In Alk-Positive Non-Small Cell Lung Cancer Patients Following Progression With Crizotinib: A Comparison Of Alectinib Phase II Data Versus Ceritinib Real-World Data (MO39246 CSR 2017).

6.46 The submission argued that the dosing applied in the clinical studies of alectinib and ceritinib was generally reflected in the 'Dosage and Administration' section of the TGA-approved Product Information (PI) for both drugs, and that PBS-subsidised alectinib and ceritinib would both be expected to be used until disease progression or development of unacceptable toxicity.

6.47 The equi-effective doses used in the cost-minimisation analysis were: 600 mg alectinib twice daily (1,200 mg/day), and 750 mg ceritinib once daily. These are the daily doses recommended in the respective PIs for the two drugs, and the doses used in the alectinib and ceritinib studies.

6.48 In claiming that the equi-effective doses are the recommended daily doses of each drug, the submission implicitly assumed that the mean duration of treatment and the mean dose intensity in clinical practice will be the same for both drugs.

6.49 If alectinib's non-inferiority to ceritinib was accepted on the basis of PFS, the implicit assumption that the mean treatment duration is the same for both drugs may be reasonable. However, if it is considered that the claim of non-inferiority is best supported by the median OS outcomes across the single-arm studies, the equi-effective doses should have been based on the mean dose and duration of treatment with which these results were obtained, i.e. taking into account any difference in the mean dose intensity and mean treatment duration between the two sets of studies. The ESC agreed with this, and considered that, in the event that the PBAC considers the cost-minimisation approach to be acceptable, it would have been more appropriate to compare the total drug cost of alectinib and ceritinib that achieves the same overall survival outcome.

6.50 As the median dose intensity in the alectinib studies (98.5% and 99.6% in NP28761 and NP28673, respectively) was higher than in the ceritinib studies (82.8% and 84.9% in ASCEND-1 and ASCEND-2, respectively), the submission may have under-estimated the equi-effective dose of alectinib relative to ceritinib on a milligram to milligram basis.

6.51 The submission proposed an ex-manufacturer price for alectinib of $[redacted], and stated that at this price the cost per day of alectinib treatment is cost-minimised to the cost per day of ceritinib treatment.

- The ESC considered that a cost-minimisation analysis based on cost per day assumes that the mean duration of treatment between the drug and its comparator was the same. However, in this case, little or no evidence was presented on the comparative durations of treatment of alectinib and ceritinib.
- The PSCR (p3, 6) claimed that the ratios of the median duration of treatment and PFS for in the phase III ALUR (for alectinib) and ASCEND-5 (for ceritinib) trials were close to unity.
- The ESC considered that the mean duration of treatment with alectinib was likely to be longer than the mean duration of treatment with ceritinib, if the submission's claim of numerical superiority in ORR, OS and PFS was taken into account. Consequently, if the price of alectinib was determined using a cost-minimisation approach based on the cost per day of treatment, the mean cost for a course of alectinib will be greater than that of ceritinib. The ESC considered

that submission has not demonstrated that the potential incremental gain in health outcomes justifies this additional cost.

- As such, the ESC considered that the submission's approach to the cost-minimisation analysis was inappropriate, and potentially biased in favour of alectinib.

6.52 Responding to the ESC's concerns, the sponsor's pre-PBAC response (p2-3) presented an alternate economic analysis considering dose intensity, treatment duration and OS outcomes from the alectinib and ceritinib trials. The pre-PBAC response claimed that this resulted in a lower drug cost per month of overall survival for alectinib based on the trials presented in the submission. The pre-PBAC response therefore argued that these results confirmed the validity of the cost-minimisation approach taken in the submission, and sought a PBAC recommendation for alectinib based on price parity with ceritinib on a cost per day of treatment basis.

6.53 The pre-PBAC response (p2) further noted that the PBAC had estimated the equi-effective doses of afatinib, erlotinib and gefitinib on the basis of the doses determined for their respective key trials without adjusting for any variations in dose intensity or treatment duration (erlotinib PSD, July 2013). In addition, the Pre-PBAC response (p.1) requested that, in the event of a recommendation to list alectinib without reference to any line of therapy, crizotinib also be included as a comparator, and thus (p.3) the price of alectinib should also reflect the price of crizotinib.

Table 10: Cost-minimisation analysis: alectinib versus ceritinib (published price)

	Alectinib	Ceritinib
Form	Capsule	Capsule
Strength	150 mg	150 mg
Pack quantity	224	150
Total mg per pack	33,000 mg	22,500 mg
Daily dose	1,200 mg	750 mg
Days of treatment per pack	28	30
Cost-minimisation, daily cost based on the AEMP		
Cost/day (AEMP)	$[redacted]	$237.61
AEMP	$[redacted]	$7,128.30
Cost/day (DPMQ)	$[redacted]	$242.54
DPMQ*	$[redacted]	$7,276.18

AEMP = approved ex-manufacturer price.
* The DPMQ includes a wholesale mark-up of $69.94, an administration fee of $70.92 and a dispensing fee of $7.02. Figures in italics were calculated during the evaluation.
Source: Table 3.3, p3 Section 3 of the submission; Alectinib Section 3 Workbook_Final.xlsx.

Drug cost/patient/course: $[redacted]

6.54 The cost/patient/course was estimated to be $[redacted]. This was calculated using the proposed published dispensed price of $[redacted] for 28 days' supply, and assuming a mean treatment duration of [redacted] weeks, based on the mean PFS in the alectinib studies NP28761 and NP28673. This was compared with $[redacted] per patient for ceritinib, based on a published dispensed price of $7,276.18 for 30 days' supply, and

assuming the same mean duration of treatment. These estimates assume a dose intensity of 100% for both drugs.

Estimated PBS usage & financial implications

6.55 This submission was not considered by DUSC.

6.56 The submission used a mixed method approach. The submission used an epidemiological approach to estimate the incidence of ALK-positive non-squamous or not otherwise specified NSCLC, based on data published by the Australian Institute of Health and Welfare and the MSAC PSD for testing of the ALK gene in patients with NSCLC (Application No. 1250, November 2013). The proportion of eligible patients assumed to receive first-line crizotinib, the proportion of patients with progressive disease who would receive second-line ALK inhibitor therapy, and the market share of alectinib was based on expert opinion from clinicians on the sponsor's clinical advisory board.

6.57 The submission estimated that there would be [redacted] patients from the sponsor's patient access program, for whom a grandfathering arrangement has been requested in the first year of listing. The submission included these patients in the cost off-sets resulting from substitution for ceritinib, which is inappropriate. The PSCR (p7) claimed that these offsets were estimated in compliance with the Departmental guidelines. The ESC considered that while the approach to the estimation of offsets using script volumes rather than patient numbers was consistent with the Departmental guidelines, the inclusion of these patients in the cost off-sets (from substitution for ceritinib) was inappropriate, as these patients were being treated with alectinib, rather than ceritinib.

6.58 The mean duration of treatment was estimated from the IRC assessed mean PFS. The mean PFS in the studies will be underestimated, as the largest observation was censored and the estimation was restricted to the largest event time. In addition, the mean PFS in the proposed Australian setting (second-line to a prior ALK inhibitor) may be longer than that observed in the studies, in which the majority of patients had previously been treated with both crizotinib and chemotherapy. The ESC considered that the clinical place of alectinib would have a significant impact on the financial implications of alectinib, as the efficacy of alectinib and consequently its mean duration of treatment, were likely to vary according to its clinical place in therapy.

6.59 The mean number of scripts per patient and, therefore, the mean cost per patient for a course of alectinib are likely to be higher than estimated in the submission, given that the mean duration of treatment, based on the estimated mean PFS in the clinical studies, is likely to underestimate the mean duration of treatment in clinical practice.

6.60 The submission assumed that all use of alectinib will substitute for use of ceritinib. The mean duration of ceritinib treatment was assumed to be the same as that for alectinib (i.e. the mean PFS in the alectinib studies). As the median PFS in the ceritinib studies (5.4-7.2 months) was numerically shorter than the median PFS in the alectinib studies (8.3 months), there is potential for the mean duration of treatment with ceritinib to be shorter than the mean duration of treatment with

alectinib. In addition, the submission did not take dose reductions for management of adverse events into account, despite highlighting the extent of dose reductions required with ceritinib in the submission. Therefore, the submission may have overestimated the cost off-sets resulting from substitution for ceritinib. The pre-PBAC response (p3) acknowledged this, but contended that any difference in budget impact would be expected to be minor in contrast to the clinical benefit for a small number of patients with a rare cancer.

6.61 The submission also estimated potential savings to the MBS resulting from the estimated net reduction in the use of MBS items associated with the use of radiotherapy to treat CNS metastases due to substitution of alectinib for ceritinib. In addition, it is likely that in many cases these costs may be deferred, rather than completely avoided.

- The PSCR (p4) claimed that the estimated cost savings resulting from a reduction in radiotherapy utilisation to manage CNS metastases was not a significant driver of the estimate of the net financial cost over listing alectinib on the PBS.
- The ESC considered that the estimated offset was uncertain, as it was based on the estimated difference in central nervous system objective response rate for alectinib over ceritinib.
- Notwithstanding the PSCR's arguments, the ESC considered that the costs associated with radiotherapy to treat CNS metastases would likely be delayed for most patients, rather than avoided, and therefore completely off-setting these costs from the financial estimates was inappropriate, and favoured alectinib.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of alectinib						
Cost to PBS/RPBS[a]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments[b]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for ceritinib						
Cost to PBS/RPBS[a]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments[b]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS/MBS	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**

[a] The discrepancy in the cost to the PBS/RPBS for alectinib and ceritinib was due to rounding of the script substitution rate and the fact that the cost-minimisation analysis was performed using the ex-manufacturer price.

[b] The discrepancy in the patient copayments for alectinib and ceritinib was due to the substitution of 1.07 packs of alectinib for 1 pack of ceritinib.

Source: Table 4.13 p13, Table 4.16 p 15, Table 4.20 p17, Table 4.21 p18 and Table 4.25, p21 Section 4 of the submission; Excel workbook Alectinib Section 4 Workbook, sheets 6 and 10.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net saving to the PBS was less than $10 million per year.

6.62 Given that the submission may have underestimated the cost per patient per course for alectinib, and may have overestimated the cost off-sets resulting from substitution for ceritinib, the proposed net financial cost to the PBS/RPBS were potentially underestimated. The ESC considered that the net financial cost to the PBS was likely to have been underestimated.

For more detail on PBAC's view, see section 7 "PBAC outcome."

7 PBAC Outcome

7.1 The PBAC recommended an Authority Required listing of alectinib for the treatment of patients with ALK-positive NSCLC, on a cost-minimisation basis against ceritinib.

7.2 In making this recommendation, the PBAC noted the relatively small population of patients with ALK-positive NSCLC and the clinical need for additional targeted therapies with different safety profiles than currently available treatments for this condition. The PBAC considered that the submission's claim of non-inferiority for efficacy and safety against ceritinib was reasonable, and therefore a cost-minimisation approach against ceritinib was appropriate.

7.3 The PBAC noted that while the submission's proposed PBS restriction positioned alectinib after crizotinib, the evidence presented in the submission was in a different setting. The PBAC recalled it had previously recommended ceritinib without any restrictions to the line of therapy for this condition, also largely on the basis of data from its use in a different setting (ceritinib Public Summary Document, November 2016 PBAC meeting). The PBAC therefore advised that the restriction criteria for alectinib should be in close alignment with the current PBS listing of ceritinib, i.e. a telephone Authority listing without any restrictions to the line of therapy.

7.4 The PBAC noted and welcomed the range of consumer comments received for alectinib which described its benefits in slowing disease progression in patients with ALK-positive NSCLC. The PBAC noted that a number of comments highlighting the benefit of alectinib were from patients with CNS metastases.

7.5 The PBAC noted that, in the naïve indirect comparison between the two pooled single-arm alectinib studies (NP28761 & NP28673) and the two pooled single-arm ceritinib studies (ASCEND-1 & ASCEND-2) presented in the submission, the difference in the point estimate of median PFS (IRC assessed) numerically favoured alectinib, with the median OS trending in alectinib's favour as well. The PBAC considered that the OS comparison was potentially confounded by differences in post-progression therapies between the studies, and that overall, the survival data was relatively immature with only 39%-43% of patients having experienced an event. Notwithstanding these and other inherent limitations of indirect comparisons between single-arm studies, the PBAC considered that on balance, the submission's claim of non-inferior comparative effectiveness against ceritinib, was acceptable.

7.6 Although the submission claimed that alectinib demonstrated higher CNS ORR, including complete responses for patients with measurable CNS metastases at baseline, the PBAC considered that it was difficult to draw meaningful conclusions regarding the extent of incremental benefit versus ceritinib, if any, on CNS response in patients with measurable CNS lesions, given the small sample sizes across both sets of studies and the indirect nature of the comparison.

7.7 The PBAC considered that, based on the data presented in the submission, alectinib and ceritinib had different side effect profiles. The PBAC noted that ceritinib was associated with a higher incidence of Grade 3-4 diarrhoea, nausea and vomiting than alectinib, while myalgia and creatinine phosphokinase elevation were prominent in the alectinib trials. The PBAC noted that [redacted] Furthermore, cases of severe interstitial lung disease/pneumonitis have been reported with both drugs. As such, the PBAC advised that, although currently available clinical data was insufficient to fully define the safety profile of alectinib, it was reasonable to conclude that it was non-inferior in terms of comparative safety, compared with ceritinib.

7.8 The PBAC noted that the PSCR (p2) and the pre-PBAC response (p1) presented the results for the investigator assessed PFS from the ALEX trial comparing alectinib versus crizotinib in treatment-naïve patients with ALK-positive advanced NSCLC. The PBAC also noted that the pre-PBAC response (p1-2) claimed that alectinib was superior to chemotherapy in relation to comparative effectiveness and safety, based on data from the phase 3 ALUR trial. However, these data were not considered in the PBAC's deliberations as they had not been independently evaluated.

7.9 The PBAC noted that while the submission's cost-minimisation approach to determine the cost of alectinib was based on the cost per day of treatment, the ESC advised that alectinib should be cost-minimised to ceritinib on the basis of the total drug cost that achieves the same overall survival outcome. The PBAC also noted that the pre-PBAC response (p2-3) presented an alternate economic analysis considering dose intensity, treatment duration and OS outcomes for the alectinib and ceritinib trials, in response to ESC's concerns. The PBAC considered that a study-based cost-minimisation analysis, allowing for the difference in PFS/treatment duration and relative dose intensity observed in the alectinib and ceritinib studies, introduced uncertainty, as (i) such an approach would be confounded by the differences in the duration of follow-up for each of the studies; (ii) both ceritinib and alectinib studies allowed patients to continue treatment beyond disease progression and; (iii) the impact of the data for treatment duration and PFS (if used as a proxy for treatment duration) being censored.

7.10 The PBAC considered that the treatment duration with ceritinib was likely to be shorter than the mean treatment duration with alectinib, given that median PFS in the ceritinib studies (5.4-7.2 months) was numerically shorter than that in the alectinib studies (8.3 months). The PBAC noted that the pre-PBAC response (p3) acknowledged this, but contended that any difference in budget impact was likely to be minor in contrast to the clinical benefit for a small number of patients with a rare cancer. On balance, the PBAC advised that, in order to reduce the financial risk to the Commonwealth, the differential duration of therapy be taken into account in

calculating the cost-minimisation approach.

7.11 The PBAC therefore advised that the effective price for alectinib be no higher than the effective price for ceritinib, on the basis of cost per day of treatment, with alectinib 600 mg (4 x 150 mg capsules) twice daily and ceritinib 750 mg (5 x 150 mg capsules) daily considered to be the equi-effective doses, also taking into account the different durations of therapy.

7.12 The PBAC rejected the request in the Pre-PBAC response (p.1) for including crizotinib as a comparator in the event of a recommendation to list alectinib without reference to any line of therapy, and thus (p.3) to reflect the price of crizotinib in the price of alectinib. The PBAC noted that, unlike ceritinib and alectinib, crizotinib required written authorisation be obtained for PBS subsidy, which means that it is increasingly less likely to be used.

7.13 The PBAC considered that the financial estimates presented in the submission were overestimated, given that the uptake rate of ceritinib since its listing on the PBS on 1 April 2017 was substantially lower than that predicted in the submission. Nonetheless, the PBAC advised that the financial estimates would need to be revised in light of its recommendation for PBS listing of alectinib for ALK-positive NSCLC without restricting the line of therapy. The PBAC considered that the revised estimates should appropriately account for patients in the sponsor's patient access program, some of whom might be eligible to receive alectinib via a grandfathering arrangement.

7.14 The PBAC noted that, as it had recommended alectinib for ALK-positive NSCLC patients without restricting the line of therapy, a streamlined co-dependent submission, requesting the corresponding change to MBS item 73341 for ALK testing, will need to be considered by the Medical Services Advisory Committee (MSAC) at its July 2017 meeting.

7.15 The PBAC advised that the Early Supply Rule should not apply to alectinib.

7.16 The PBAC advised that alectinib was not suitable for prescribing by nurse practitioners.

7.17 The PBAC advised that, under subsection 101(3BA) of the National Health Act, 1953 alectinib should not be treated as interchangeable on an individual patient basis with any other drugs.

7.18 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:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
ALECTINIB			
Alectinib 150 mg capsule, 224	1	1	Alecensa® Roche Products Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ 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:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ 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:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ 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:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐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 develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
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	№.of Rpts	Proprietary Name and Manufacturer
ALECTINIB Alectinib 150 mg capsule, 224	1	1	Roche Products Pty Ltd Alecensa

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐ Optometrists ☐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:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date]; AND The treatment must be as monotherapy AND Patient must have a WHO performance status of 2 or less AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.

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.
Prescriber Instructions	A patient may qualify for PBS-subsidised treatment under this restriction once only.
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.

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

Roche welcomes the PBAC's decision to recommend alectinib for patients with advanced ALK-positive NSCLC and are working with the Department of Health towards a PBS listing at the earliest opportunity.