7.02 CABOZANTINIB, Tablet 20 mg, 40 mg, and 60 mg, Cabometyx®, Ipsen Pty Ltd.

1 Purpose of submission

1.1 The resubmission requested a Section 85, Authority Required (Streamlined) listing of cabozantinib in patients with stage IV clear cell variant advanced renal clear carcinoma (RCC), with intermediate to poor risk classification according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, and who have not been previously treated with a tyrosine kinase inhibitor (TKI). The current listing for cabozantinib allows use in patients who have already received treatment with a TKI (irrespective of IMDC risk classification).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus sunitinib.

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

Component	Description
Population	Patients with stage IV clear cell variant advanced RCC, with ECOG status of 0-2 and intermediate to poor risk classification who have not been previously treated with a TKI.
Intervention	Cabozantinib 60 mg, 40 mg or 20 mg orally once daily until disease progression or unacceptable toxicity.
Comparator	Sunitinib 50 mg orally once daily for the first 4 weeks of consecutive 6 week cycles, until disease progression or unacceptable toxicity
Outcomes	Progression free survival (PFS), objective response rate (ORR) and overall survival (OS)
Clinical claim	In adults with stage IV RCC, ECOG status of 0-2, with intermediate to poor risk disease according to IMDC criteria who have not been treated with a TKI, compared to sunitinib, cabozantinib provides: • Significantly superior PFS and ORR with a trend towards improved OS; and • Different but broadly comparable safety.

Source: Table 1.2, p. 31 of the resubmission.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium criteria; RCC = renal cell carcinoma; TKI = Tyrosine-kinase inhibitor.

2 Background

Registration status

2.1 Cabozantinib is TGA-registered for the treatment of RCC in adults:
- who are treatment-naïve with intermediate or poor risk RCC; and
- following prior treatment with vascular endothelial growth factor targeted therapy.

Previous PBAC consideration

2.2 Cabozantinib was rejected by the PBAC at its March 2019 meeting for use in treatment-naïve patients with advanced RCC on the basis that the magnitude of the clinical benefit in terms of PFS was uncertain due to the small sample size and high

risk of bias in the clinical trial, and the PBAC noted there was no demonstrated benefit in OS or safety in the comparison of cabozantinib versus sunitinib. The PBAC considered that the revised ICER for cabozantinib versus sunitinib, based on the PBAC's preferred assumptions, was high (paragraph 7.1, cabozantinib, PSD, March 2019 PBAC meeting). A summary of the key matters of concern from the March 2019 meeting and whether they were addressed in the current resubmission is presented in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical place in therapy	PBAC noted that there may be a clinical role for cabozantinib in the second-line setting following NIVO+IPI (i.e. removing the requirement in the existing listing for use to be post-TKI). The PBAC noted that no evidence was presented for use of cabozantinib following NIVO+IPI, but similarly, there is limited prospective evidence for sunitinib or pazopanib post-immunotherapy (Para 7.3, March 2019 PSD).	Addressed in amended restriction by not requiring use to be post-TKI. Evidence provided in the resubmission for cabozantinib use post immunotherapy relied largely on single-arm observational studies post-TKI with limited comparative evidence to sunitinib or pazopanib.
Clinical claim: cabozantinib vs sunitinib	For treatment-naïve patients, the PBAC considered the magnitude of the clinical benefit in terms of PFS was uncertain due to the small sample size and high risk of bias in the clinical trial, and the PBAC noted there was no demonstrated benefit in OS or safety (Para 7.1, March 2019 PSD).	Not addressed. No additional data from CABOSUN were provided to support the claim of superior PFS or OS compared to sunitinib.
Economic evaluation approach: treatment naïve setting	The PBAC considered that, given the uncertain and likely small increase in PFS versus sunitinib, an alternative approach could be a CMA versus sunitinib (Para 7.17, March 2019 PSD).	Not addressed. The resubmission presented a CUA to sunitinib in the treatment-naïve setting only. A CMA to sunitinib and pazopanib was prepared by the evaluators. The ESC re-iterated that a higher price may not be adequately justified in this setting given the PFS benefit observed in CABOSUN appeared small and was likely overestimated, and an improvement in OS was not supported.
Economic approach: first TKI post-immunotherapy	In settings where there is no RCT evidence of superiority, the PBAC considered that a higher cost for cabozantinib versus sunitinib may be difficult to justify (Para 7.18, March 2019 PSD).	Not addressed. The resubmission requested a higher price than sunitinib in the first TKI post-immunotherapy setting, despite the lack of RCT evidence in this setting. The ESC considered that a higher price may not be adequately justified in this setting given the lack of robust data to support superiority versus sunitinib or pazopanib.
Economic evaluation	Post-progression costs were over-estimated, particularly in the sunitinib arm, due to the inclusion of non-PBS listed drugs (Para 7.11, March 2019 PSD).	Not adequately addressed. The resubmission adopted an alternative approach to estimating post-progression costs by using data from a 10% PBS sample of patients receiving first-line sunitinib/pazopanib to estimate post-progression costs. The rationale for this approach was not adequately justified, particularly as current PBS use does not reflect treatment following progression on cabozantinib in the proposed setting.

Component	Matter of concern	How the resubmission addresses it
Economic evaluation	Post-progression costs were over-estimated … due to the assumption that patients who receive subsequent therapies continue to be treated until death (Para 7.11, March 2019 PSD)	Addressed. The resubmission applied the proportion of time that patients receive post-progression treatment; however, in applying this to data from the 10% PBS sample which were based on actual treatment exposure the resubmission over-corrected (underestimated) for the reduction in treatment costs prior to death.
Economic evaluation	The PBAC recommended the base case of the modelled analysis should be re-specified using: (i) a time horizon of 7.5 years; (ii) convergence of OS, PFS and TTD beginning at 30 months, with convergence at 7.5 years; (iii) average patient weight of 80 kg; and (iv) the same costs (per cycle) of subsequent treatment in the cabozantinib and sunitinib arms (Para 7.12, March 2019 PSD). The PBAC also considered that the revised base case ICER (i.e. revised using the assumptions outlined above) was very high and the cost for cabozantinib would need to be reduced substantially to bring the ICER into an acceptable range (Para 7.13, March 2019 PSD).	Adequately addressed for the time horizon and convergence of curves and patient weight (though the ESC noted that patient weight was now irrelevant as no weight-based drugs were included in the base case of the analysis). The resubmission did not apply the same costs of subsequent (post-progression) therapy across the treatment groups. The ESC maintained that the same costs should be applied in each arm given the lack of reliable alternative data. The price of cabozantinib in the proposed new settings (treatment-naïve and TKI-naïve post-immunotherapy) was reduced by 35% from the March 2019 submission.
Financial estimates	The submission did not address the potential changes in use of other PBS listed treatments including the impact on current use of cabozantinib in the post-TKI setting that may arise from its use in the first-line setting and the potential for increased use of other medicines (in subsequent lines of therapy) that would be affected by availability of a first-line treatment for patients with poor risk (Para 6.59, March 2019 PSD).	Addressed for post-TKI setting cabozantinib and substituted first-line sunitinib and pazopanib, noting the change in the price for cabozantinib in the proposed setting relative to its current listing. However, the PBAC considered the offsets were not reliably estimated.

Source: Compiled during the evaluation using 6.02 cabozantinib March 2019 Public Summary Document.
Abbreviations: CMA = cost-minimisation analysis; CUA = cost-utility analysis; NIVO+IPI = nivolumab plus ipilimumab; OS = overall survival; PFS = progression-free survival; PSD = Public Summary Document; TKI = tyrosine kinase inhibitor; TTD = time-to-treatment discontinuation;

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

3 Requested listing

3.1 The restriction requested in the submission is outlined below. The PBAC's suggested changes are not incorporated into the restriction text, given the PBAC considered that a combined treatment line-agnostic listing would be more appropriate (refer to Paragraph 3.5).

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
CABOZANTINIB Tablet 20 mg, 40 mg, and 60 mg, 30	30	2 (initial) 5 (continuing)	$9,952.12 published $[redacted] effective	Cabometyx® Ipsen Pty Ltd

Category/Program:	General Schedule/Section 85
PBS indication:	Stage IV clear call variant renal cell carcinoma (RCC)
Treatment phase:	Initial
Restriction:	Streamlined

Clinical criteria:	The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC); AND Patient must have a WHO performance status of 2 or less; AND The patient must not have previously been treated with any tyrosine kinase inhibitor; AND The treatment must be the sole PBS-subsidised tyrosine kinase inhibitor therapy for this condition.
Prescriber criteria:	Patients who have developed intolerance to sunitinib or pazopanib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised cabozantinib. Patients who have progressive disease with pazopanib or sunitinib are not eligible for PBS-subsidised cabozantinib under this restriction.

Abbreviations: PBS = Pharmaceutical Benefits Scheme.

Category/Program:	General Schedule/Section 85
PBS indication:	Stage IV clear call variant renal cell carcinoma (RCC)
Treatment phase:	Continuing treatment beyond 3 months
Restriction:	Streamlined
Clinical criteria:	Patient must have received an initial authority prescription for this drug for this condition; AND Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST); AND The treatment must be the sole PBS-subsidised tyrosine kinase inhibitor therapy for this condition.
Prescriber criteria:	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. Patients who have developed progressive disease on pazopanib or sunitinib are not eligible to receive PBS-subsidised cabozantinib under this PBS restriction.

Abbreviations: PBS = Pharmaceutical Benefits Scheme.

3.2 The resubmission requested a special pricing arrangement with an effective DPMQ for cabozantinib of $[redacted] and published DPMQ of $9,952.12 per 30 tablets for all three strengths (60 mg, 40 mg and 20 mg). Cabozantinib is currently listed in the post-TKI setting with an effective DPMQ of $[redacted] and a published DPMQ of $9,952.12 per 30 tablets for all three strengths.

3.3 The effective price for the proposed new settings (treatment-naïve and TKI-naïve post-immunotherapy) is [redacted]% lower than in the March 2019 submission ($[redacted] per 30 tablets).

3.4 The resubmission proposed a broader restriction than in the March 2019 submission. The resubmission's restriction would allow use in:

- Treatment-naïve patients – previously untreated patients with poor or intermediate risk classification by IDMC criteria. This is unchanged from the previous submission and aligns with the TGA indication. The PBAC previously considered that the patients most likely to receive cabozantinib in this setting would be those for whom immunotherapy is deemed inappropriate.
- TKI-naïve post-immunotherapy patients – patients who have previously received immunotherapy and who have poor or intermediate risk classification by IDMC criteria. While this is broader than the TGA-registered indications for cabozantinib (which are for use in "treatment-naïve adults with intermediate or poor risk" and "following prior treatment with vascular endothelial growth factor targeted therapy" which includes TKIs), the ESC considered that it would be clinically reasonable for cabozantinib to be used in any treatment line for RCC.

3.5 The PBAC considered that there was no clinical rationale for having separate listings for cabozantinib in the requested and existing settings, and that a combined 'line-agnostic' listing for cabozantinib would reflect the likely use of cabozantinib given the changes to the treatment algorithm. Further, the ESC noted there is a risk of use under the incorrect item code (refer to 'Financial Management – Risk Sharing Arrangements' section regarding the potential for a weighted price).

3.6 The existing listing is for patients of any prognostic risk according to the IMDC criteria, while the proposed restriction is only for patients with intermediate to poor risk RCC, which the PBAC considered to be appropriate because:

- Treatment-naïve patients - this aligns with the key evidence presented in the submission, the CABOSUN trial.
- TKI-naïve post-immunotherapy patients - the PBAC noted that these patients are likely to have intermediate to poor risk disease based on the IMDC criteria given that they have already received immunotherapy and subsequently progressed.

3.7 The requested restriction included the criterion: "Patients who have developed intolerance to sunitinib or pazopanib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised cabozantinib". Given the likelihood of patients who have developed an intolerance to a prior TKI also having tolerability issues with cabozantinib, the PBAC considered that this would not be appropriate to include in the cabozantinib restriction.

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

4 Population and disease

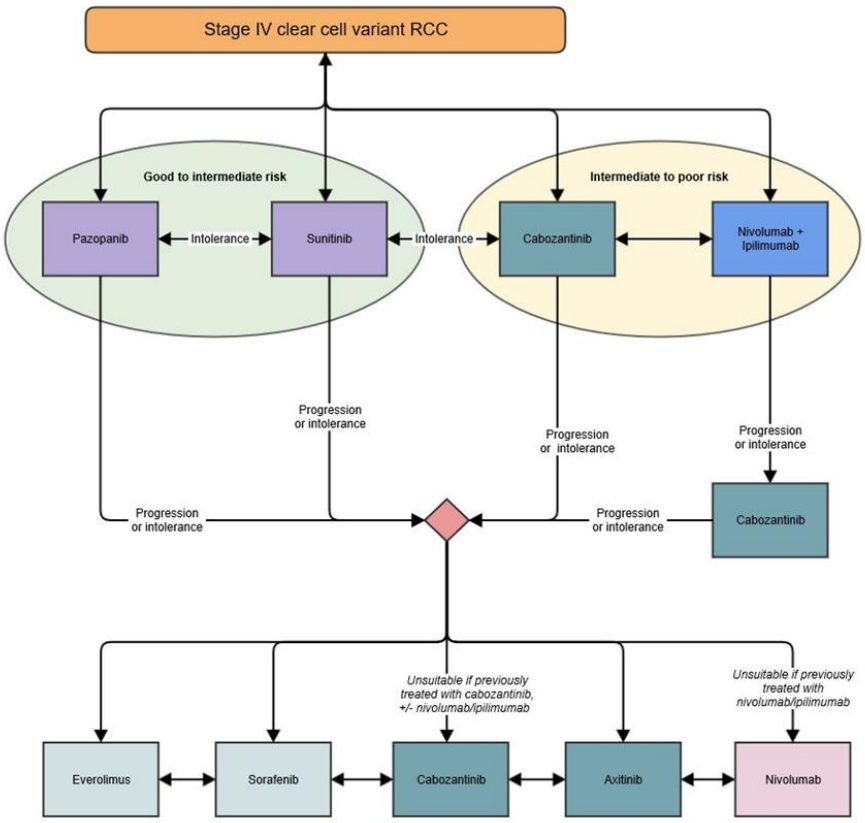
4.1 RCC is a type of cancer originating from the lining of renal tubules of the kidney. It is the most common form of kidney cancer accounting for 80-90% of all cases. It has been estimated that the incidence of kidney cancer was 3,617 new cases in 2018 representing 2.6% of all new cancer cases, with 1,069 deaths associated with this tumour type (Cancer Australia 2018; paragraph 4.2, cabozantinib, Public Summary Document (PSD), March 2019 PBAC meeting).

4.2 Cabozantinib is for use in patients with clear cell variant stage IV RCC, an ECOG performance status of 0 to 2 and intermediate or poor risk classification based on IMDC criteria. The target population comprises patients who have not received treatment with a TKI but who may have been treated with an immunotherapy regimen such as nivolumab and ipilimumab (hereafter referred to as NIVO+IPI).

4.3 Cabozantinib is a TKI. The resubmission proposed (see Figure 1) that cabozantinib would be used as the first TKI, irrespective of prior immunotherapy exposure, in patients with intermediate to poor risk disease. The proposed clinical algorithm and the requested restriction do not specifically address the immunotherapy inappropriate population. During evaluation it was considered that patients who are

unsuitable for immunotherapy may include patients with an autoimmune disease. The Pre-Sub-Committee Response (PSCR) stated that patients for whom regular travel to hospitals for infusions is challenging and patients in whom PD-L1 expression of their tumour is less than 1% would also be considered unsuitable for immunotherapy. The financial estimates assumed that the immunotherapy inappropriate (unsuited) population would comprise 10% of the first-line population (i.e. patients who are unable to receive NIVO+IPI).

Figure 1: Proposed clinical management algorithm



Source: Figure 1.2, p.40 of the resubmission.
The proposed listings of cabozantinib are in the first two rows. The bottom row reflects the existing listing of cabozantinib. It was unclear why the axitinib box is the same colour as the cabozantinib boxes. The restriction for axitinib is the same as that for sorafenib and everolimus (and cabozantinib in the existing setting) and requires prior use of a TKI.

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

5 Comparator

5.1 The submission nominated sunitinib as the main comparator. This was reasonable as the PBAC accepted sunitinib as the main comparator in the March 2019 submission (paragraph 7.4, cabozantinib PSD, March 2019 PBAC Meeting).

5.2 Pazopanib was listed on a cost-minimisation basis against sunitinib and remains a potentially relevant comparator for pricing purposes.

5.3 Sunitinib and pazopanib are listed on the PBS for use in RCC patients of favourable to intermediate risk (but not in patients at poor risk), while the proposed restriction for cabozantinib is for patients at intermediate to poor risk. The PBAC has previously acknowledged that sunitinib (and pazopanib) are used in clinical practice in patients who are at poor risk and accepted sunitinib as the appropriate comparator in its consideration of NIVO+IPI (paragraph 5.3, Nivolumab plus ipilimumab, PSD, July 2018 PBAC meeting).

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 organisations (2) via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from Rare Cancers Australia, who considered that the listing would increase equity of access, and that cabozantinib was associated with improved outcomes, is well tolerated and has low burden on patients' quality of life.

6.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the cabozantinib submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the CABOSUN trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for cabozantinib, 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 sunitinib.

Clinical studies

6.4 The primary clinical evidence presented for the treatment-naïve setting was the CABOSUN trial (N=157), a phase II, randomised, controlled, multi-centre, open-label, trial comparing cabozantinib with sunitinib in patients with previously untreated advanced or metastatic clear cell RCC. This was unchanged from the March 2019 submission.

6.5 The resubmission also presented clinical evidence for cabozantinib used as the first TKI post-immunotherapy and as the second (or subsequent) TKI post-immunotherapy. Cabozantinib is already listed on the PBS for use as the second (or subsequent) TKI and thus, the evidence for use in this setting was not considered during the evaluation.

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

6.6 There were six studies identified as evidence for cabozantinib in the first TKI post-immunotherapy setting including four non-randomised studies (MD Anderson CC; N = 70, Taussig/Barts; N = 33, DFCI 2; N = 6, and City of Hope; N = 11), one exploratory analysis of an RCT (CheckMate214 subsequent; N = 33), and one study of unknown design (DFCI 1; N = 69). Details of the included studies are provided in Table 3. There were no other potentially relevant studies identified during the evaluation.

Table 3: Studies and associated reports presented in the resubmission

Trial ID Other ID	Protocol title/ Publication title	Publication citation
Treatment-naïve therapy		
CABOSUN (NCT01835158 (A031203)	Clinical study report (CSR). Choueiri, T. K., Halabi, S., Sanford, B. et al. 2016. "PR CABOzantinib versus SUNitinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups: results from ALLIANCE A031203/CABOSUN trial." Choueiri TK, Halabi S, Sanford BL et al. 2017. "Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203/CABOSUN Trial Choueiri, T. K., Hessel, C., Halabi, S. et al. 2018. "Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203/CABOSUN randomised trial): progression-free survival by independent review and overall survival update."	31 July 2017 Annals of oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO 2016. Denmark. 27 J Clin Oncol 35 (6): 591-597 European J Cancer 94:115-125.
TKI-naïve post-immunotherapy		
MD Anderson CC	(Shah et al. 2019) "Outcomes of patients with metastatic clear-cell renal cell carcinoma treated with second-line VEGFR-TKI after first-line immune checkpoint inhibitors. (Shah AY et al. 2018) "Outcomes of patients (pts) with metastatic clear-cell renal cell carcinoma (mCCRCC) treated with second-line (2L) vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKI) after first-line (1L) immune checkpoint inhibitors (ICI)."	Eur J Cancer 114:67-75. J Clin Oncol 36 (no.6_suppl (February 20 2018)):682-682. Poster at ASCO 2018.
DFCI 1	(McGregor BA et al. 2018) "Activity of cabozantinib (cabo) after PD-1/PD-L1 immune checkpoint blockade (ICB) in metastatic clear cell renal cell carcinoma (mccRCC)." (Lalani et al. 2019) "Activity of cabozantinib after PD-1/PD-L1 immune checkpoint blockade in metastatic clear-cell renal cell carcinoma."	European Society for Medical Oncology website, accessed 2/4/19. Poster at ESMO 2018. Canadian Urological Association Journal 13 (2 Supplement 2):S13. Poster at CUOS 2019.
Taussig / Barts	(Barata, A, et al. 2018) "The efficacy of VEGFR TKI therapy after progression on immune combination therapy in metastatic renal cell carcinoma." (Barata, De Liano, et al. 2018) "Clinical outcome of patients (PTS) with metastatic renal cell carcinoma (mRCC) progressing on front-line immune-oncology based combination (IO-COMBO) regimens."	Br J Cancer 119:160-163. Journal of Clinical Oncology 36 (6 Supplement 1). Poster at ASCO 2018.

Trial ID Other ID	Protocol title/ Publication title	Publication citation
	(Barata, Gomez de Liano, et al. 2018) "Clinical outcome of patients with metastatic Renal Cell Carcinoma (mRCC) progressing on front-line combination regimens that include checkpoint inhibitors."	Kidney Cancer 2 (Supplement 1):S10-S11. Poster – 16th International Kidney Cancer Symposium 2017
DFCI 2	(Martini et al. 2018) "Durable clinical benefit in metastatic renal cell carcinoma patients who discontinue PD-1/PD-L1 therapy for immune-related adverse events."	Cancer Immunology Research 6 (4):402-408.
CheckMate214 subsequent	(Auvray et al. 2019) "Second-line targeted therapies after nivolumab-ipilimumab failure in metastatic renal cell carcinoma."	European Journal of Cancer 108:33-40.
City of Hope	(Dizman et al. 2019) "Targeted Therapies Following First-Line Immune Checkpoint Inhibitor Combination in Metastatic Renal Cell Carcinoma: A Single Center Experience."	Kidney Cancer Pre-press (Pre-press):1-6.

Source: Table 2.3, p.54-55 of the resubmission.

6.7 The key features of CABOSUN (which was conducted in treatment-naïve patients) and the six studies for cabozantinib in TKI-naïve patients post-immunotherapy are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias[b]	Patient population	Outcomes	Use in modelled evaluation
Cabozantinib vs sunitinib (treatment-naïve therapy)						
CABOSUN	157	R, OL 25 months	High risk for performance bias; moderate for remaining criteria.	Previously untreated patients with advanced or metastatic clear cell RCC, having intermediate to poor risk classification by IDMC criteria	PFS, OS, ORR, AE	PFS, OS, AE
Cabozantinib (TKI-naïve post-immunotherapy)						
MD Anderson CC	70	OB	Moderate	Patients with metastatic clear cell RCC who progressed after being treated with first-line immunotherapy and were subsequently treated with a second-line VEGFR-TKI	PFS, OS, ORR	Not used
DFCI 1	69	Unknown	Moderate	Patients with metastatic clear cell RCC who received cabozantinib after progression on immunotherapy	PFS [a], OS, ORR	Not used
Taussig/Barts	33	OB	Moderate	Patients with metastatic clear cell RCC having progression and were subsequently treated with at least one VEGFR-TKI.	PFS, ORR	Not used
DFCI 2	6	OB	Moderate	Patients who discontinued immunotherapy due to development of an immune-related adverse event	ORR	Not used
CheckMate214 subsequent	33	OB	Moderate	Patients with clear cell metastatic RCC treated with immunotherapy (nivolumab+ipilimumab) as part of Checkmate214 and who received any subsequent treatment with VEGFR TKIs	PFS, OS, ORR	Not used
City of Hope	11	OB	Moderate	Patients who received first-line combination treatment with immune checkpoint inhibitor for treatment of metastatic RCC	PFS, OS, ORR	Not used

Source: Table 2.3, p.5-6 of the Attachment 3 of the resubmission; developed during the evaluation

Abbreviations: AE = adverse event; IDMC = International Metastatic RCC Database Consortium; OB = observational study: OL = open label; ORR = objective response rate: OS = overall survival; PFS = progression-free survival; R = randomised; RCC = renal cell carcinoma; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitors

Note: [a] time to treatment failure

[b] Risk of bias in CABOSUN and the six studies included for TKI naïve post-immunotherapy were assessed using different systems (Cochrane for CABOSUN and ROBIN 1 for the TKI naïve post-immunotherapy studies). Due to a lack of available information on the TKI naïve post-immunotherapy studies, several domains of the risk for bias criteria were classified as "No Information" according to the Robin 1 tool. These differences in tools and data completeness confound the comparison of the risk of bias across CABOSUN and the six cohort studies.

6.8 The PBAC previously noted that CABOSUN enrolled a relatively small number of patients and the PFS results assessed by the IRC were more favourable to cabozantinib than those from the (Alliance) investigator assessment (paragraphs 6.10 and 7.5, cabozantinib, PSD, March 2019 PBAC meeting).

6.9 For the studies in which cabozantinib was used as the first TKI post-immunotherapy, there was limited information provided regarding patient characteristics, study design, approach used for analysis of clinical outcomes and treatments used. Five of the six studies (MD Anderson CC, Taussig/Barts, DFCI 2, CheckMate215 subsequent, and City of Hope) included data for other TKIs in addition to cabozantinib and did not separately report baseline characteristics of patients receiving cabozantinib. All patients from DFCI 1 received cabozantinib post-immunotherapy, however, patient characteristics were inadequately reported (e.g. gender, performance score, location of metastases were not reported) as only a conference abstract was available from the study. Overall, the available information was insufficient to assess the extent of homogeneity across the studies and their consistency with the proposed PBS population.

6.10 The ESC recalled that the PBAC had "previously noted the advice during the consumer hearing was that there are no prospective trials of cabozantinib in this setting and that similarly, there is limited prospective evidence for sunitinib or pazopanib post-immunotherapy" (para 7.3, cabozantinib, PSD, March 2019 PBAC meeting).

Comparative effectiveness

Treatment-naive therapy

6.11 Results for key clinical outcomes including progression free survival (PFS), overall survival (OS), objective response rate (ORR), and safety from CABOSUN were unchanged from the March 2019 submission. Additional analyses of data from CABOSUN were provided in the resubmission including more results from subgroup analyses of PFS, an exploratory analysis of effect according to PD-L1 expression, and an analysis of health-related quality of life based on ECOG score. Overall, results from these analyses were consistent with the results from the key clinical outcomes.

6.12 The PFS results from CABOSUN are presented in Table 5. These data indicated a PFS advantage for cabozantinib with a hazard ratio (HR) of 0.48 (95% CI: 0.31, 0.74) for IRC-assessed PFS and 0.66 (95% CI: 0.46, 0.95) for investigator-assessed PFS.

Table 5: Results of progression-free survival - CABOSUN

	Cabozantinib		Sunitinib		Difference in median, mths	p value[a]	HR (95% CI)
	n/N (%)	Median mths (95% CI)	n/N (%)	Median mths (95% CI)			
IRC assessed-September 2016 data-cut-off.	43/79 (54)	8.6 (6.8, 14.0)	49/78 (63)	5.3 (3.0, 8.2)	3.3	**0.00**	**0.48 (0.31, 0.74)**
Investigator assessed-April 2016 data cut-off.	NR[b]	8.2 (6.2, 8.8)	NR[b]	5.6 (3.4, 8.1)	2.6	**0.01**	**0.66 (0.46, 0.95)**

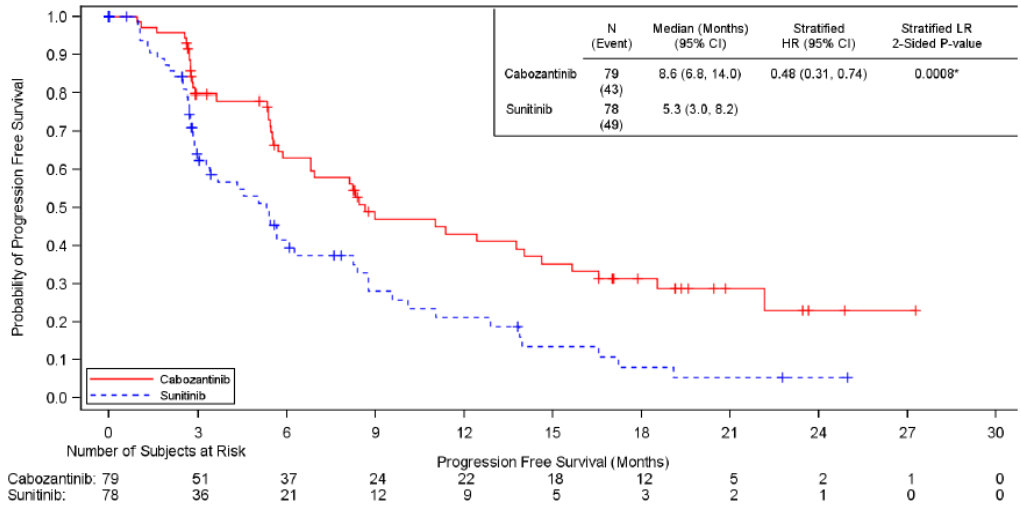
Sources: Table 2.11, p.23; Table 2.12, p.24; of Attachment 3 of resubmission.
Abbreviations: CI= confidence interval; HR= hazard ratio; IRC = Independent Radiographical Committee; n = number of participants with event; N = total participants in group; NR = not reported; mths = months; PFS = progression free survival.
Notes: [a] Log-rank p-value (stratified); [b] Total PFS events were 123; Statistical differences noted in bold.

6.13 The PBAC previously considered that CABOSUN showed a statistically significant improvement in PFS for cabozantinib, but considered the magnitude was uncertain and likely overestimated as the trial had a high risk of bias due to the open-label design

and imbalances in missing data, with substantial differences in the investigator-assessed and IRC analyses of PFS (para. 7.5, cabozantinib, PSD, March 2019 PBAC meeting).

6.14 The resubmission claimed that the issue of imbalance in missing data (with more patients having missing data in the sunitinib arm) was unlikely to affect the results. The resubmission stated that this was because unevaluable patients in the sunitinib arm had worse prognostic factors than those who remained in the sunitinib arm, due to more of the unevaluable patients being of poor risk, of an age over 65 years, ECOG PS of 2, having had a prior metastectomy, prior radiotherapy or with bone metastases. Therefore, it was unlikely that the inclusion of unevaluable patients would have improved the treatment effect for the sunitinib arm. The evaluation considered that this appeared reasonable; however, the data on the poorer prognosis of those unevaluable patients were not verifiable within the clinical study report provided by the resubmission.

Figure 2: Kaplan-Meier Plot of PFS (IRC-determined/FDA-recommended censoring rules; ITT population)



Source: Figure 2-14, p.25 of Attachment 3 of the resubmission.

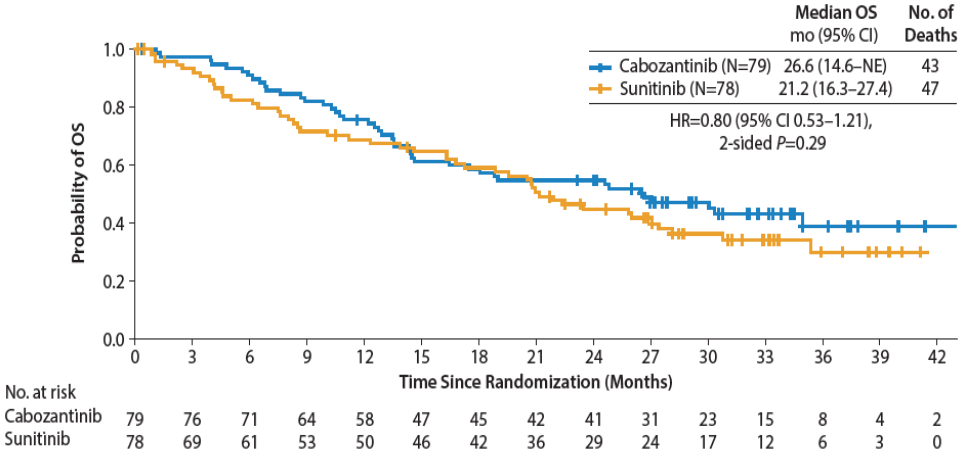
6.15 The resubmission did not provide updated OS data. As outlined in Table 6, there was no statistically significant difference in OS for either the earlier data cut-off of September 2016 (HR=0.74; 95% CI: 0.47, 1.14) or the more recent data cut-off of July 2017 (HR=0.80; 95% CI: 0.53, 1.21).

Table 6: Results of overall survival - CABOSUN

	Cabozantinib		Sunitinib		Difference in median, mths	p value[a]	HR (95% CI)
	n/N with event (%)	Median mths (95% CI)	n/N with event (%)	Median mths (95% CI)			
September 2016 cut-off.	38/79 (48)	30.3 (14.6, NE)	45/78 (58)	21.0 (16.3, 27.0)	9.3	0.17	0.74 (0.47, 1.14)
July 2017 cut-off.	43/79 (54)	26.6 (14.6, NE)	47/78 (60)	21.2 (16.3, 27.4)	5.4	0.29	0.80 (0.53,1.21)

Sources: Table 2.20, p.34; Figure 2.16, p.35 of Attachment 3 of the resubmission.
Abbreviations: CI= confidence interval; HR= hazard ratio; n = number of participants with event; N = total participants in group; NE = not estimable mths = months;
Notes: [a] Log-rank p-value (stratified)

Figure 3: Kaplan-Meier plot of OS in CABOSUN (July 2017; ITT population)



Source: Figure 2-16, p.35 of Attachment 3 of the resubmission.

6.16 The PBAC previously noted that CABOSUN demonstrated a numerical improvement in OS for cabozantinib versus sunitinib but the difference was not statistically significant and appeared to be decreasing with additional follow-up. The PSCR argued that there is a strong correlation between treatment effects on PFS and OS, and that the PFS benefit may translate into prolonged survival. However, the ESC considered that this claim was not adequately justified and re-iterated the PBAC's previous advice that "the submission's claim that there was a trend towards improved OS was not supported by the evidence presented" (para 7.6, cabozantinib, PSD, March 2019 PBAC meeting).

6.17 The OS results may be confounded by subsequent anticancer treatments utilised by a high proportion of patients in both groups, together with the imbalance in types of treatments received in the respective study groups within CABOSUN. The direction of bias is uncertain given the lack of details provided on outcomes following subsequent treatments (para. 6.20, cabozantinib, PSD, March 2019 PBAC meeting). There were no additional data provided by the resubmission to address this issue.

<u>TKI-naïve post-immunotherapy</u>

6.18 A summary of the PFS results for cabozantinib as the first TKI post-immunotherapy compared with its use in treatment-naïve patients (CABOSUN) is presented in Table 7.

Table 7: PFS with cabozantinib and other TKIs in the treatment-naïve and TKI-naive post-immunotherapy settings

Study ID Source	TKI	n/N (%)	Median PFS months (95% CI)	PFS rate 1 year (%)
Treatment-naïve setting				
CABOSUN	Cabozantinib	43/79 (54)	8.6 (6.8, 14.0)	43
	Sunitinib	49/78 (63)	5.3 (3.0, 8.2)	21
TKI-naïve post-immunotherapy setting				
Cabozantinib results reported separately to other TKIs				
MD Anderson CC (Shah et. 2019)	TKI [a, c]	33/70 (47)	13.2 (10.1, -)	53
	Cabozantinib	-/20	15.2 (7.9, NR)	-
	Sunitinib [c]	-/6	3.6 (0.9, NA)	-
	Pazopanib [c]	-/19	24.4 (6.1, NA)	-
	Axitinib [c]	-/25	13.2 (8.6, NA)	-
DFCI 1 (McGregor BA et al. 2018)	TKI	-	-	-
	Cabozantinib	-/69	6.6 (5.3, 8.5) [b]	-
Combined TKI results reported only				
Taussig / Barts (Barata et al. 2018)	TKI [a]	-/33	6.41 (4.4, 8.4)	-
	Cabozantinib	-/4	NR	-
CheckMate214 subsequent (Auvray et al. 2019)	TKI [a]	-/33	8 (5, 13)	-
	Cabozantinib	-/2	-	-
City of Hope (Dizman et al. 2019)	TKI [a]	-/11	7.7 (4.6, 10.8)	-
	Cabozantinib	-/5	-	-

Source: 2.39, p.99 of the resubmission; Table 2.11, p.23; Table 2.12, p.24 of Attachment 3 of the resubmission; Table 3, p.72 of Shah et al. 2019

Abbreviation: CI = confidence interval; n = number of participants with event; N = total participants in group; NA = not applicable; NR = not reached; PFS = progression free survival; TKI = tyrosine-kinase inhibitor.

Note: [a] Including cabozantinib; [b] time to treatment failure (TTF); [c] Figures were retrieved during evaluation.

6.19 MD Anderson CC reported a numerically higher median PFS with cabozantinib than the CABOSUN trial (15.2 months; 95% CI 7.9, NR vs 8.6 months; 95% CI 6.8, 14.0). DFCI 1 provided numerically lower median PFS compared to CABOSUN (6.6 months; 95% CI 5.3, 8.5 vs 8.6 months; 95% CI 6.8, 14.0). Other studies including Taussig/Barts, CheckMate214 subsequent, and City of Hope had a small number of patients receiving cabozantinib and only reported the results for all TKIs combined.

6.20 A summary of the OS results for the use of cabozantinib as the first TKI post-immunotherapy compared with cabozantinib in CABOSUN is presented in Table 8.

Table 8: OS with cabozantinib and other TKIs in the treatment-naive and first TKI post-immunotherapy settings

Study ID Source	TKI	n/N (%)	Median OS months (95% CI)	OS rate 1 year (%; 95% CI)
Treatment-naïve setting				
CABOSUN	Cabozantinib	38/79 (48)	30.3 (14.6, NE)	76
	Sunitinib	45/78 (58)	21.0 (16.3, 27.0)	69
TKI-naïve post-immunotherapy setting				
Cabozantinib results reported separately to other TKIs				
MD Anderson CC (Shah et. 2019)	TKI [a, b]	22/70 (31)	NR	80 (70, 90)
	Cabozantinib	-/20	NR	74 (54, 100)
	Sunitinib[b]	-/6	NR	33 (11, 100)
	Pazopanib[b]	-/19	NR	89 (75, 100)
	Axitinib[b]	-/25	NR	87 (74, 100)
DFCI 1 (McGregor BA et al. 2018)	TKI	-	-	-
	Cabozantinib	-/69	-	53 (37, 66) [b]
Combined TKI results reported only				
CheckMate214 subsequent (Auvray et al. 2019)	TKI [a]	-/33	13.0 (8.0, NR)	54
	Cabozantinib	-/2	-	-
City of Hope (Dizman et al. 2019)	TKI [a]	6/11	22.7 (10.9, 4.3)	36[b]
	Cabozantinib	-/5	-	-

Source: 2.39, p.99 of the resubmission; Table 2.20, p.34; Table 2.20, p.34 of Attachment 3 of the resubmission; Table 3, p.72 of Shah et al. 2019

Abbreviation: CI = confidence interval; n = number of participants with event; N = total participants in group; NA = not applicable; NR = not reached; OS = overall survival; TKI = tyrosine-kinase inhibitor.

Note: [a] Including cabozantinib; [b] Figures were retrieved during evaluation

6.21 OS with cabozantinib at 1 year in the MD Anderson CC study was similar to that in CABOSUN (74%; 95% CI: 54% to 100% vs 76%; 95% CI NA to NA). Overall, there were insufficient results for OS from the post-immunotherapy studies to be able to draw any meaningful comparison between OS outcomes from these studies with the OS results from CABOSUN.

6.22 While there is low-quality evidence to suggest that cabozantinib is active in TKI-naïve patients post-immunotherapy, the commentary and the ESC considered that the absolute and relative benefit is unknown given:

- None of the studies presented were designed to specifically investigate the use of cabozantinib as the first TKI post-immunotherapy.
- There was no evidence presented which informed a comparison of cabozantinib with sunitinib in the proposed treatment setting (there was no comparator arm in the studies presented in this setting).
- The studies presented were relatively small, single arm, cohort studies which were potentially heterogeneous. There was limited information available and presented for these studies, greatly limiting the extent to which any available evidence could be combined.
- The resubmission did not present a translation study to demonstrate that any comparative treatment effect for cabozantinib (or TKIs) in the post-immunotherapy setting would be applicable in the proposed treatment-naïve or first-line setting, or vice versa.

Comparative harms

Treatment-naïve therapy

6.23 A summary of the key adverse events reported in CABOSUN is provided in Table 9. The key adverse events remained unchanged from the March 2019 submission. The PBAC previously noted that the safety data from CABOSUN indicated that diarrhoea, hypertension and hypothyroidism were more common for patients treated with cabozantinib compared to sunitinib, however the safety data were based on a small number of patients. Overall the PBAC previously considered that cabozantinib and sunitinib appear to have broadly comparable overall safety profiles (para. 7.7, cabozantinib, PSD, March 2019 PBAC meeting).

Table 9: Summary of key adverse events in CABOSUN

n (%)	Cabozantinib n (%) N=78	Sunitinib n (%) N=72	RD (95% CI)
	Any grade	**Any grade**	**Any grade**
Solicited AEs			
Diarrhoea	57 (73)	39 (54)	**0.19 (0.04, 0.34)**
Hypertension	52 (67)	32 (44)	**0.22 (0.06, 0.38)**
AST increased	47 (60)	22 (31)	**0.30 (0.14, 0.46)**
ALT increased	43 (55)	20 (28)	**0.27 (0.12, 0.43)**
Neutrophil count decreased	12 (15)	25 (35)	**-0.19 (-0.33, -0.06)**
Unsolicited AEs reported in >15% patients in either treatment arm			
Weight decreased	25 (32)	12 (17)	**0.15 (0.02, 0.29)**
Hypothyroidism	18 (23)	4 (5.6)	**0.18 (0.06, 0.29)**
Dysphonia	17 (22)	1 (1.4)	**0.20 (0.10, 0.31)**
Alopecia	14 (18)	2 (2.8)	**0.15 (0.05, 0.25)**
Dermatitis acneiform	12 (15)	2 (2.8)	**0.13 (0.03, 0.22)**
White blood cell count decreased	9 (12)	25 (35)	**-0.23 (-0.37, -0.10)**

Source: Table 2.37, p.51; Table 2.38, p.52 of the Attachment 3 of the resubmission.
Abbreviations: AEs = adverse events; CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk
Note: Statistical differences noted in bold. The evaluators estimated risk difference (RD and 95% CI) for each types of AEs. AEs that were considered 'expected' per the protocol and presence/absence and severity were referred as solicited while other AEs were collected as unsolicited events (the CSR p.9).

TKI-naïve post-immunotherapy

6.24 Safety data were either not reported (DFCI 1, and DFCI 2), or were not reported separately for cabozantinib (MD Anderson, Taussig/Barts, ChectMate214 subsequent, and City of Hope) in the post-immunotherapy setting. The most commonly reported AEs for patients receiving TKIs post-immunotherapy were fatigue and diarrhoea. The resubmission noted that "while the information about the safety profile of the included TKIs was minimal from the supportive studies, the reported toxicity is consistent with the magnitude and type of adverse event associated with the known safety profile of cabozantinib". Fatigue and diarrhoea were also commonly found in patients receiving cabozantinib and TKIs (sunitinib) in the first-line setting.

Benefits/harms

6.25 A summary of the comparative benefits and harms for cabozantinib versus sunitinib in the treatment-naïve setting is presented in Table 10. This remained unchanged from the March 2019 submission. Given the nature of the studies presented for the use of cabozantinib as the first TKI post-immunotherapy and the lack of comparative data versus sunitinib, it was not possible to form a statement of comparative benefits and harms for cabozantinib to sunitinib in that setting.

Table 10: Summary of comparative benefits and harms for cabozantinib versus sunitinib: treatment-naïve setting

Benefits					
Progression free survival (median duration of follow up 25 months)					
Event	**Cabozantinib**	**Sunitinib**	**Absolute Difference**		**HR (95% CI)**
Progressed, n (%)	40/79 (54)	43/78 (63)	-		**0.48 (0.31, 0.74)**
% not progressed at 12 months (95% CI)	43.1 (NR)	21.1 (NR)	22.0		-
Overall survival (median duration of follow up 28.9 months)					
Deaths, n (%)	38 (48)	45 (58)	-		0.74 (0.47, 1.14)
Harms (median duration of follow up 25 months)					
Potentially clinically relevant adverse events (any grade)	**Cabozantinib (n=78)**	**Sunitinib (n=72)**	**Events/100 patients**		**RD % (95% CI)**
			Cabozantinib	**Sunitinib**	
Diarrhoea	57	39	73	54	**0.19 (0.04, 0.34)**
Hypertension	52	32	67	44	**0.22 (0.06, 0.38)**
Hypothyroidism	18	4	23	5.6	**0.18 (0.06, 0.29)**
Neutrophil	12	25	15	35	**-0.19 (-0.33, -0.06)**

Source: Compiled during the evaluation
Abbreviations: n=number; CI, confidence interval; NR=not reported; RD = risk difference; RR = risk ratio
Note: Statistical differences noted in bold. Progression was defined by IRC assessment.

6.26 On the basis of the direct evidence presented by the resubmission, for every 100 patients treated with cabozantinib in comparison with sunitinib in the treatment-naïve setting:

- Approximately 22 additional patients will be progression-free at 12 months.
- Approximately 19 additional patients will experience diarrhoea.
- Approximately 22 additional patients will experience hypertension (high blood pressure).
- Approximately 18 additional patients will experience hypothyroidism (an underactive thyroid gland).
- Approximately 19 fewer patients will experience a decreased neutrophil count (low white blood cell count).

Clinical claim

Treatment-naïve therapy

6.27 The clinical claim for use in the treatment-naïve setting remained unchanged from the March 2019 submission. The resubmission described cabozantinib as significantly superior in PFS and ORR, with a trend towards improved OS compared with sunitinib.

6.28 The PBAC re-iterated its previous consideration that the clinical claim with regard to PFS was adequately supported by the evidence presented but considered the magnitude was uncertain and likely overestimated given the small number of patients enrolled and issues of potential bias (due to the open-label design and the differences in the investigator-assessed and IRC analyses of PFS). The PBAC considered that the claim for a trend towards improved OS was not supported by the evidence presented.

TKI-naive post-immunotherapy

6.29 In the first TKI post-immunotherapy setting, the resubmission described cabozantinib as significantly superior in PFS and ORR, with a trend towards improved OS (i.e. the same clinical claim as in the treatment-naïve setting).

6.30 The evaluation and the ESC considered there was a paucity of data available to support this claim, but similarly noted that there is limited prospective evidence for sunitinib or pazopanib post-immunotherapy. Acceptance of the claim made in the resubmission would rely on extrapolation of the evidence from CABOSUN in the treatment naïve setting to use as the first TKI post-immunotherapy setting. The ESC agreed with the commentary that in the absence of a translational study to support the clinical benefit of cabozantinib across the different settings, it remained unclear as to whether cabozantinib post-immunotherapy would result in the same benefit as in the naïve treatment setting.

6.31 In the TKI-naive post-immunotherapy setting, the PBAC considered that the claim of superior comparative effectiveness was not adequately supported given the paucity of data available.

Safety

6.32 In both settings, the resubmission claimed that cabozantinib has different but broadly comparable safety compared with sunitinib. The PBAC considered this was reasonable.

Economic analysis

6.33 While the resubmission presented a cost-utility analysis versus sunitinib, the ESC considered that a cost-minimisation analysis (CMA) versus sunitinib or pazopanib may have been appropriate noting that the PBAC previously considered that a CMA could be an alternative approach given the uncertain and likely small increase in PFS (para 7.17, cabozantinib, PSD, March 2019 PBAC meeting), and that no new clinical evidence had been presented. The previous PSD further stated “Given the small and uncertain

PFS benefit and the absence of a demonstrated OS benefit or improvement in QoL for cabozantinib versus sunitinib in the first-line setting, the PBAC considered that any future submission requesting use in a broader setting (e.g. a combined "line agnostic" listing) would need to be based on conservative assumptions. In settings where there is no RCT evidence of superiority, the PBAC considered that a higher cost for cabozantinib versus sunitinib may be difficult to justify" (para 7.18, cabozantinib, PSD, March 2019 PBAC meeting).

6.34 A CMA versus sunitinib was conducted by the evaluators. The results, based on the resubmission's assumed effective prices, are presented below.

Table 11: Cost-minimisation analysis between sunitinib and cabozantinib (based on prices assumed in submission)

	Sunitinib	Cabozantinib
AEMP assumed in submission	$[redacted] for 37.5 mg, 28 tablets $[redacted] for 50 mg, 28 tablets	$[redacted], 60/40/20 mg, 30 tablets
Estimated average dose per day treated (mg)	43.70 (CABOSUN) [a]	49.40 (CABOSUN)
Days of treatment	28 days of 42 days cycle (67%)	No treatment breaks (100%)
1.Cost-minimisation based on mean duration of treatment		
Mean duration of treatment (months) [b]	7.2	12.6
Cost per course	$[redacted]	$[redacted]
Cabozantinib price required for cost-min	-	[redacted]% price reduction (AEMP of $[redacted])
2.Cost-minimisation based on same average price per day		
Effective AEMP per day	$[redacted] [b]	$120.00
Cabozantinib price required for cost-min	-	[redacted]% price reduction (AEMP of $[redacted])

Source: developed during the evaluation

Abbreviations: AEMP = approved ex-manufacturer price; mg = milligram

Note: [a] In the economic model, the resubmission estimated that 50.4% and 49.6% of patients would use sunitinib 37.5 mg and 50 mg, respectively (to achieve averaged dose per day at 43.7 mg). [b] mean treatment duration is based on economic model extrapolations.

[b] This is the average cost per day during the treatment course (regardless of whether sunitinib is administered that day, noting that sunitinib is given 28 days of a 42 day cycle).

6.35 Two alternative approaches to the CMA were presented in the evaluation. The first approach set the total cost per patient for cabozantinib to be equal to that for sunitinib ($[redacted]/patient), and so takes into account the mean treatment duration with cabozantinib and sunitinib. This would require a [redacted]% reduction to the requested AEMP for cabozantinib (using the resubmission's assumed effective prices). The second approach set the daily cost for cabozantinib to be equal to the average daily cost for sunitinib ($[redacted]/day) and this would require a [redacted]% reduction to the requested AEMP for cabozantinib (using the resubmission's assumed effective price). The different prices for cabozantinib with the two methods is due to the different treatment durations with an average treatment duration of 12.6 months for cabozantinib compared with only 7.2 months for sunitinib.

CUA model presented in submission

6.36 The resubmission presented a CUA comparing cabozantinib with sunitinib as outlined in Table 12. The PBAC previously proposed a re-specified base case for the CUA using: (i) a time horizon of 7.5 years; (ii) convergence of OS, PFS and TTD beginning at 30 months, with convergence at 7.5 years; (iii) average patient weight of 80 kg; and (iv) the same costs (per cycle) of subsequent treatment in the cabozantinib and sunitinib arms (para 7.12, cabozantinib, PSD, March 2019 PBAC meeting). The resubmission incorporated assumptions (i)-(iii) into the economic model, however included a new analysis for the subsequent treatment after progression which did not align with the suggested assumption (iv). These were the four key changes implemented in the CUA included in the resubmission.

6.37 The evidence for cost-effectiveness provided in the resubmission assessed the use of cabozantinib in the treatment-naive setting only. It did not assess the use of cabozantinib:

- as the first TKI post-immunotherapy (which is part of the requested listing), or
- specifically in immunotherapy inappropriate patients (the patient group most likely to use cabozantinib in the treatment-naïve setting).

The cost-effectiveness of cabozantinib in these settings could not be assessed using the submitted economic model.

6.38 The PSCR argued that there is a paucity of data available for cabozantinib in the first TKI post-immunotherapy setting, and that it is biologically plausible that cabozantinib would retain a clinical benefit compared to sunitinib as the first TKI post-immunotherapy. As such, the PSCR claimed that the economic model based on the CABOSUN trial in treatment-naïve patients is suitable for modelling purposes. The ESC considered that it was unclear whether cabozantinib would demonstrate the same incremental benefit in the first TKI post-immunotherapy setting as was shown in the treatment-naïve setting (in CABOSUN). Further, the economic model would be in a different treatment setting (e.g. use post-immunotherapy would represent a later-line to the modelled scenario, and thus patient characteristics may change and the post-progression treatments and durations would differ). Thus, the ESC considered that the cost-effectiveness of cabozantinib in this setting is unknown. The financial estimates predicted that around 75% of patients in the requested listing would be in the first TKI post-immunotherapy setting (based on Table 20).

Table 12: Key components of the economic evaluation

Component	March 2019 submission: original	March 2019 submission: PBAC's preferred assumption	Resubmission
Type of analysis	Cost-utility analysis	-	Unchanged
Outcomes	Cost per quality adjusted life years gained and cost per life year gained	-	Unchanged
Time horizon	10 years	7.5 years	7.5 years
Convergence of OS, PFS and TTD	No	Beginning at month 30 to 7.5 years with convergence at 7.5 years	Beginning at month 30 to 7.5 years with convergence at 7.5 years
Average weight of patients	89.7 kg	80 kg	80 kg. The ESC noted this change was consistent with PBAC's advice, but noted that it was no longer necessary given no weight-based medicines were considered in the base case analysis.
Post-progression disease costs	Subsequent therapies based on use as reported in CABOSUN (treatment group specific)	Same costs (per cycle) of subsequent treatment in the cabozantinib and sunitinib arms as per CABOSUN	Based on 10% PBS data of patients starting sunitinib/pazopanib as first-line treatment
Method(s) used to generate results	Partitioned survival model	-	Unchanged
Health states	Stable disease, progressive disease, death	-	Unchanged
Cycle length	Four weeks (28 days), half cycle corrected	-	Unchanged
Health state movements	Based on survival curves for PFS and OS from CABOSUN (individual patient data). Time to treatment discontinuation estimates applied for a costing-based scenario analysis	-	Unchanged. The ESC noted that a difference in OS was modelled despite the PBAC previously considering that a difference in OS was not supported by the clinical data.
Quality of life	Based on estimates from the literature. Utility values: PFS = 0.77; PD = 0.72; AE disutility = -0.04.	-	Unchanged. The ESC previously considered the utilities were from a study that appeared to have a healthier population than the likely PBS population (Para 6.42, March 2019).
Resource utilisation	Based on the available literature, review of published economic models.	-	Unchanged
Software	Microsoft Excel 2010	-	Unchanged

Source: Table 3-2, p. 159 of the resubmission

Abbreviations: kg = kilogram; PBS = Pharmaceutical Benefits Scheme; PFS = progression-free survival; OS = overall survival; RCC = renal cell carcinoma; TTD = time to treatment discontinuation

Post-progression costs

6.39 The March 2019 submission estimated the post-progression costs using CABOSUN-based data. The PBAC previously considered that the post-progression costs were overestimated and not reasonable, particularly in the sunitinib arm, due to the inclusion of non-PBS listed drugs and the assumption that patients who receive

subsequent therapies continue to be treated until death (para 7.11, cabozantinib, PSD, March 2019 PBAC meeting). The resubmission provided a new analysis for post-progression costs using PBS-based data from a 10% sample of RCC patients (n=132) initiated on sunitinib or pazopanib on the PBS from January 2013 to June 2019, who were dispensed other drugs for RCC after sunitinib or pazopanib (Table 13). Patients were grouped according to whether or not they had received cabozantinib as a subsequent treatment, which the submission stated was because patients treated with cabozantinib would not be eligible for further treatment with cabozantinib in later lines. To estimate the cost of therapy post-cabozantinib, the analysis excluded patients who received immunotherapy (nivolumab) as a subsequent treatment to reflect that cabozantinib is likely to be used in patients who are inappropriate for immunotherapy and thus unlikely to receive subsequent nivolumab.

6.40 The resulting assumed post-progression therapies are outlined in the table below.

Table 13: Number of patients receiving each post-progression treatment by treatment arm in the model

Medicine	CABOSUN (n=157)		10% PBS Full analysis (n=132)			10% PBS Excluding immunotherapy (n=51)		
	Cabozantinib (n=NR)	**Sunitinib (n=NR)**	**Cabozantinib (n=111)**	**Sunitinib (n=21)**	**Combined (n=132)**	**Cabozantinib (n=44)**	**Sunitinib (n=7)**	**Combined (n=51)**
Nivolumab	10 (21%)	12 (26%)	67 (60%)	14 (67%)	81 (61%)	0 (0%)	0 (0%)	0 (0%)
Cabozantinib	1 (2%)	5 (11%)	0 (0%)	21 (100%)	21 (16%)	0 (0%)	7 (100%)	7 (14%)
Axitinib	18 (38%)	15 (32%)	38 (34%)	9 (43%)	47 (36%)	22 (50%)	3 (43%)	25 (49%)
Everolimus	6 (13%)	15 (32%)	30 (27%)	6 (29%)	36 (27%)	28 (64%)	2 (29%)	30 (59%)
Sorafenib	1 (2)	2 (4%)	4 (4%)	1 (5%)	5 (4%)	3 (7%)	1 (14%)	4 (8%)
Cost per cycle [a]	$ [redacted] [b]	$ [redacted] [b]	$ [redacted]	$ [redacted]	**$ [redacted] [c]**	**$ [redacted]**	$ [redacted] [d]	$ [redacted]
Use in model					Sunitinib arm	Cabozantinib arm	(d)	

Source: Table 3.36, p.199 of the resubmission; compiled during the evaluation based on Excel model

Abbreviation: PBS = Pharmaceutical Benefits Scheme; n = number of patients; NR = not reported

Note: Bold text indicated the figures used in the base case analysis; patients might receive more than one type of medicine as subsequent treatment; [a] without the proportion of time receiving treatment adjustment; [b] based on the PSCR of March 2019 submission that excluded non-PBS medicines; [c] Value applied in the base case of the model submitted for post-progression cost for sunitinib (see CELL J36 of worksheet '1. Cabo Patients (Sunitinib)'), and which results in the ICERs reported in the results section of the submission; [d] Appropriately not used in the base case of the model, despite being described as being used in the base case in the main body of the resubmission.

6.41 Post-progression costs used in the previous model (informed by post-progression treatment patterns observed in CABOSUN) and the current model (based on PBS-based data) are summarised in Table 14.

Table 14: Comparison of post-progression treatment costs applied in the previous and current submission

	Previous model (informed by post-progression treatment patterns observed in CABOSUN)		Current submission: post progression costs based on PBS 10% sample (base case economic model)	
	Cabozantinib	**Sunitinib**	**Cabozantinib**	**Sunitinib**
% patients who receive subsequent therapy	63%	67%	85%	85%
Most common treatments used post-progression, (proportion of patients), cost per cycle	Axitinib (38%), $[redacted] Pazopanib (28%), $[redacted] Nivolumab (21%), $[redacted] Temsirolimus (21%), $[redacted] Sunitinib (21%), $[redacted] Everolimus (13%), $[redacted]	Axitinib (32%), $[redacted]; Everolimus (32%), $[redacted] Nivolumab (26%), $[redacted] Sunitinib (21%), $[redacted] Pazopanib (19%), $[redacted] Bevacizumab (11%), $[redacted] Cabozantinib (11%), $[redacted]	Everolimus (64%), $[redacted] Axitinib (50%), $[redacted]	Nivolumab (61%); $[redacted] Cabozantinib (16%), $[redacted], Axitinib (36%), $[redacted] Everolimus (27%), $[redacted]
% of post-progression time on subsequent therapies	100% used in the economic model (not reported from CABOSUN)	100% used in the economic model (not reported from CABOSUN)	51%	53%
Cost per cycle (post-progression drug costs)	$[redacted] [a]	$[redacted] [a]	$[redacted]	$[redacted]
Months of post-progression treatment	20.5 from the economic model (not reported from CABOSUN)	24.5 from the economic model (not reported from CABOSUN)	7.1	11.6
Avg post-progression cost/patient	$[redacted] [a]	$[redacted] [a]	$[redacted]	$[redacted]

Source: developed during the evaluation using the Excel model from the resubmission
Abbreviation: PBS = Pharmaceutical Benefits Scheme
Note: [a] based on the PSCR of March 2019 submission that excluded non-PBS medicines

6.42 The ESC considered that a key issue with the submission's approach was that post-progression costs in the cabozantinib arm were informed by PBS data from patients treated with sunitinib/pazopanib (but who did not receive subsequent cabozantinib or immunotherapy). The ESC considered there was no evidence this would reflect post-progression treatment patterns for patients treated with cabozantinib in the treatment-naïve setting. Other key issues included:

- the 10% PBS sample was based on data from January 2013 to June 2019, and thus may not reflect current patterns of use. For example, cabozantinib was PBS-listed for use after another TKI (referred to as use "post-TKI") in June 2018 and nivolumab monotherapy was PBS-listed in August 2017.
- not all patients included in the 10% PBS sample would be eligible for first-line cabozantinib, particularly given differences in eligibility for cabozantinib and sunitinib/pazopanib based on risk status.

- the approach assumed that the pattern of care post cabozantinib (as first-line therapy) would be the same as that for other TKIs, which may not be the case given differences in AE profiles.
- exclusion of patients who received subsequent immunotherapy (nivolumab) was not reasonable as nivolumab is PBS listed for use following TKIs. The PSCR stated "the intent of the economic model was not only to represent those patients who were inappropriate for immunotherapy, but also those patients who had already been treated with combination immunotherapy as their first treatment option". However, the ESC considered that this was inconsistent with the clinical data applied in the model which was in the treatment-naïve setting. Overall, the ESC considered the applicability of these data for the cabozantinib arm was unknown.

6.43 The resubmission's analysis continued to result in a difference in post-progression costs per cycle between the cabozantinib and sunitinib arms (higher in the sunitinib arm, Table 13). The ESC considered that the higher post-progression cost per cycle in the sunitinib arm was inappropriate given the lack of applicable data on which to base any difference and that, in the absence of more reliable data, it would have been more appropriate to apply the same post-progression cost per cycle to each arm, as previously recommended by the PBAC.

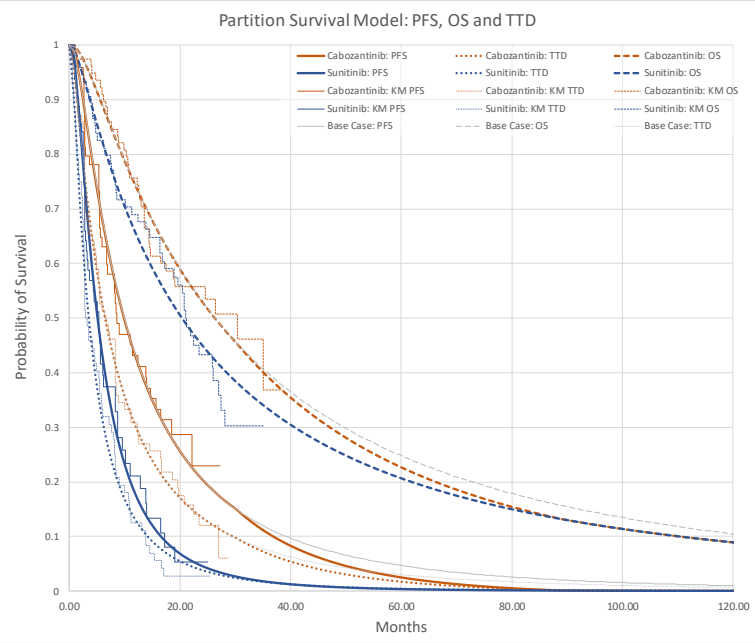
6.44 Since the analysis estimated post-progression costs on the basis of PBS exposure it took into account cessation of treatment prior to death, thereby addressing the PBAC's previous concern that post-progression costs in the model had been accumulated until the time of death. However, the resubmission unnecessarily applied a time factor for the proportion of time receiving treatment for the post-progression costs; the PBS data presented capture time on therapy and thus did not require an additional adjustment for exposure time in order to be applied in the model. The PSCR noted that this reduced the ICER from $45,000 – $75,000 per QALY to $15,000 – $45,000 per QALY and stated this "ought to be the new base case". The ESC considered that removal of the additional adjustment for treatment duration is reasonable, however noted that the revised base case as proposed in the PSCR also requires acceptance of the different post progression costs by treatment arm sourced from the 10% PBS analysis.

<u>Extrapolation</u>

6.45 The results from the extrapolations for PFS, OS, and TTD applied in the base case analysis for cabozantinib and sunitinib are outlined in Figure 4. Several issues regarding the approach used for extrapolation were previously noted by the PBAC including that: the extrapolation of outcomes was based on a small number of patients with limited follow-up time leading to uncertain outcomes; the chosen parametric distributions were not sufficiently justified; and the modelled OS did not reliably reflect the KM OS curve from the CABOSUN trial (para 7.10, cabozantinib, PSD, March 2019 PBAC meeting). Given these uncertainties, the PBAC considered that converging the OS, PFS and TTD over time should be applied in the model beginning at 30 months,

with convergence at 7.5 years (para 7.12, cabozantinib, PSD, March 2019 PBAC meeting). The resubmission addressed these issues by applying convergence into the model as previously suggested by the PBAC.

Figure 4: Base case extrapolations for PFS, OS and TTD based on CABOSUN



Abbreviations: KM= Kaplan Meier, PFS = progression free survival; OS= overall survival; TTD = time to treatment discontinuation
Source: Figure 3.16, p. 200 of the resubmission.

6.46 The ESC noted that a gain in overall survival was estimated in the model (mean of 0.27 life years gained) and considered that this may not be appropriate given the PBAC's previous concerns that the submission's claim of a trend towards improved OS was not supported by the evidence presented (para 7.6, cabozantinib, PSD, March 2019 PBAC meeting).

6.47 The key model drivers are presented in Table 15, with the model results in Table 16. The results are based on the cabozantinib effective prices and the resubmission's assumed effective prices for sunitinib and subsequent treatments. The ICER/QALY will change if the effective price of the comparator and subsequent therapies are applied.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted]/QALY gained.
Post-progression costs	Higher post-progression costs for sunitinib arm than cabozantinib	High, favors cabozantinib: using the same post-progression costs per cycle (PBS 10%) increased the ICER to $[redacted] [a]
OS	Extrapolation of OS results from CABOSUN which were not statistically significantly different.	High, favors cabozantinib. Removing the modelled OS difference results in a high ICER (>$[redacted] per QALY using the base case submitted) but also increases the sensitivity of the model to the post progression costs.

Source: developed during the evaluation using Section 3 - Economic model (Cabozantinib vs Sunitinib).
Abbreviations: ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; PBS = Pharmaceutical Benefit Scheme
Note: [a] same post-progression costs per cycle based on combined cabozantinib and sunitinib arms, including immunotherapy

Table 16: Results of the economic evaluation (assumed effective prices as per the resubmission)

	Cabozantinib	Sunitinib	Increment
Costs	$[redacted]	$[redacted]	$[redacted]
Life years	2.74	2.47	0.27
QALYS	2.03	1.81	0.23
Incremental cost per life year gained			$[redacted]
Incremental cost per QALY gained			$[redacted]
Previous consideration (March 2019)			
Incremental cost per life year gained			$[redacted]
Incremental cost per life QALY gained			$[redacted]

Source: Table 3.45, p.208 of the resubmission.
Abbreviations: ICER= incremental cost effectiveness ratio; LYG = life years gained; QALYs= quality adjusted life years

6.48 The results of key sensitivity analyses are summarised in Table 17. The model was most sensitive to the inclusion of an OS difference and the post-progression costs.

Table 17: Sensitivity analyses conducted during the evaluation

	Sensitivity analysis	Δ costs	Δ QALYs	ICER (per QALY gained)
Base case		$[redacted]	0.23	$[redacted]
1	Remove duplicated proportion of time receiving treatment: **PSCR base case**	$[redacted]	0.23	$[redacted]
2	No difference in OS (both arms based on OS in the sunitinib arm)	$[redacted]	0.03	$[redacted]
3	Post-progression costs: same cost per cycle for sunitinib and cabozantinib arms, based on combined arms full 10% sample (including immunotherapy)	$[redacted]	0.23	$[redacted]
Multivariate sensitivity analyses				
1 & 3	Remove duplicated proportion of time receiving treatment AND Same post-progression costs per cycle for sunitinib and cabozantinib arms: based on combined arms full 10% sample (including immunotherapy)	$[redacted]	0.23	$[redacted]
1 & 2 & 3	Remove duplicated proportion of time receiving treatment AND No difference in OS AND Same post-progression costs per cycle for sunitinib and cabozantinib arms: based on combined arms full 10% sample (including immunotherapy)	$[redacted]	0.03	$[redacted]

Source: Developed during the evaluation using Section 3 - Economic model (Cabozantinib vs Sunitinib).
Abbreviations: Cabo = cabozantinib; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; PBS = Pharmaceutical Benefit Scheme; PSCR = Pre-Sub-Committee Response; Suni = sunitinib.

6.49 The evaluation conducted sensitivity analyses using the same post-progression costs for cabozantinib and sunitinib. The ICER increased to $75,000/QALY – $105,000/QALY if the same post-progression costs per cycle were applied, based on the combined post-progression costs for cabozantinib and sunitinib arm (i.e. post-progression costs of less than $10 million per cycle, based on all patients from the 10% PBS sample including immunotherapy). The ESC considered these to be the most appropriate post-progression costs.

6.50 The PBAC considered that the inclusion of an OS gain was not adequately supported by the evidence. Removal of the difference in OS increases the ICER (more than $200,000/QALY) and increases the sensitivity of the model to the post progression costs. The PBAC noted the results of a multivariate sensitivity analysis which: assumed no difference in OS; removed the duplicated proportion of time receiving post-progression treatment, and applied the same post-progression costs per cycle for the sunitinib and cabozantinib arms. This resulted in an ICER of more than $200,000/QALY based on the submission's assumed effective prices.

Drug cost/patient/course $[redacted]

6.51 The average time on treatment estimated from the model was 12.6 months for cabozantinib and 7.2 months for sunitinib. Based on the resubmission's estimates, the drug cost/patient/course for cabozantinib was estimated to be $[redacted] compared to $[redacted] from the March 2019 submission. The reduction was mainly because of the lower effective price proposed in the resubmission. The drug cost per patient for the proposed and comparator drugs are summarised in Table 18.

Table 18: Drug cost per patient for cabozantinib and sunitinib

	Cabozantinib – treatment-naïve setting			Sunitinib		
	Trial dose and duration	**Model**	**Financial estimate**	**Trial dose and duration**	**Model**	**Financial estimates**
Mean dose (mg/day)	Flat pricing across strengths			43.7	43.7	37.1 [b]
Mean duration (months)	9.4[a]	12.6	10.0	5.7 [a]	7.2	8.0
Cost per patient for 30 day supply	$[redacted]		$[redacted]	$[redacted]		$[redacted]
Adjustments to drug cost	Treatment interruptions: 2.67%		-	Treatment interruptions: 0.06% Dosing schedule: 4 weeks on, 2 weeks off every 6 weeks		Dosing schedule: 4 weeks on, 2 weeks off every 6 weeks
Adjusted cost/patient/month	$[redacted]		$[redacted]	$[redacted]		$[redacted]
Cost/patient/course	$[redacted]	$[redacted] [b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 2.32, p.45 of Attachment 3 *of the resubmission*; p.45; Table 4.9, p.224 of the resubmission; Table 36, p.121 of the CSR; Section 3 - Economic model (Cabozantinib vs Sunitinib); Excel spreadsheet 'Epidemiology model', sheet 'Control Panel'; Excel spreadsheet ' Section 4 cost and utilisation model', Sheet '2d. Scripts – market' and ' 4b. Impact – changed (EFF)

Note: [a] Truncated means from CABOSUN; [b] The financial estimates were based on the proportion of use of each sunitinib strength that was used on the PBS from August 2018 to July 2019 (the value in the above table was calculated using sum-product of Rows 22 to 29 of '4b. Impact- changed (EFF)' worksheet

Estimated PBS usage & financial implications

6.52 This resubmission was not considered by DUSC. The resubmission presented a mixed market and epidemiological-based approach with the approach outlined in Table 19. This was a change from the March 2019 submission in which an epidemiological approach was presented. The approach in the resubmission was presented as a patient flow in which treatment use was based on patient months rather than patient numbers. The use of patient months, rather than patient numbers, appeared unnecessary and resulted in calculation of the financial estimates being overly

complex. During evaluation, patient numbers were calculated based on the mean time on treatment assumed in the financial estimates.

6.53 The table below shows a simplified calculation of the submission's financial estimates.

Table 19: Key inputs for the financial estimates

Assumption	Value	Year 6	Source
Total first-line Stage IV RCC market			
Australian population		28,311,405	ABS
Incidence Rate (per 100,000)	14.2		Unable to verify the value used. Likely overestimated as an incidence rate of 12.9 was stated in AIHW Cancer in Australia 2019 report.
% of kidney cancer that is RCC	90%		Unclear source. DUSC June 2014 review estimated 85%.
% Stage IV	30%		Unclear source. DUSC June 2014 review estimated 25%.
Total Stage IV incident patients		1,085	
Relapsed earlier stage incident patients			
Earlier stage patients		2,533	Potentially unnecessary step. Stage IV incident patients were already accounted for in the incidence approach used.
Relapse rate from early stages	23%		
Total relapsed earlier stage patients		583	
Total eligible (incident + relapsed)		**1,668**	
1L Treatment rate	80%		Source not able to be verified.
Pts treated 1L Stage IV RCC		**1,334**	
Favourable Patients	13%	167	Tran et al. 2018
Intermediate Patients	60%	804	
Poor Patients	27%	364	
Patients treated with cabozantinib (for proposed listing)			
A. Treatment-naïve population (Intermediate-poor risk patients unsuitable for IO)			
Unsuitable for immunotherapy	10%	117 [a]	(i.e. 10% of intermediate-poor risk patients)
Cabozantinib market share (1L IO inappropriate patients)	100%	117 [a]	Assumes 100% of intermediate-poor risk patients who are unsuitable for IO will receive cabo (no suni or pazo use)
Treatment duration in 1L (months)	10 months		Unclear source, 12.6 months in economic model
B. Relapse post 1L NIVO+IPI (TKI-naïve post-immunotherapy)			
Treated with NIVO+IPI	90%	1,051 [a]	(i.e. 90% of treated intermediate-poor risk patients).
1L patients who progress to 2L	80%	841	Unclear source. Assumes 80% of all patients treated with NIVO+IPI relapse and receive 2L TKI.
Cabozantinib market share (post IO)	50%	420 [a]	Remaining 50% were assumed to receive suni or pazo
Treatment duration post IO	8 months		Unclear source
Offsets			
Cabozantinib offsets (reductions to use in existing setting)			
1. Relapse post 1L TKI (no IO)			
% who relapse post 1L TKI (1L to 2L)	80%		As above, unclear source
% who receive cabozantinib in status quo	40%		Appears to be based on assumed market share when NIVO monotherapy was a comparator. Appeared to also be applied to favourable risk patients,
Treatment duration in this setting	9 months		PBS 10% sample, but uses median rather than mean (mean was 13.6 months)
2. Relapse post 2nd TKI (i.e. 3L post IO)			
% who progress 2L to 3L and are treated	60%		Unclear source. Appeared to be applied to intermediate risk patients only.
Treatment duration 3L cabozantinib	7 months		Unclear source

Source: Excel spreadsheet 'Epidemiology model', Table 4.9, p.228 of the resubmission. Excel spreadsheet 'Section 4 cost and utilisation model'

Abbreviations: 1L = first-line; 2L = second-line; 3L = third-line; ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; IO = immunotherapy; TKI = tyrosine kinase inhibitor .
[a] These were calculated during preparation of the PBAC Minutes, based on the underpinning assumptions.

6.54 The estimated use of cabozantinib in the requested settings was likely overestimated as:

- the assumptions used to estimate the incidence of kidney cancer, the proportion of patients with RCC and the proportion diagnosed with stage IV disease were higher than those available elsewhere in the literature (likely overestimated the eligible patient population).
- the resubmission assumed that 23% of patients with earlier stage disease (Stage I-III) would relapse into stage IV and be eligible for treatment. This step may not have been necessary with the incidence approach used, as these patients are already included in the incident stage IV population. As such, this step likely double-counted patients and overestimated the eligible population.
- these assumptions used to calculate the treatment-naive population flowed-on through the treatment algorithm, and thus overestimated the TKI-naïve post-immunotherapy population.

6.55 The financial estimates begin in Month 6 of Year 1, so Year 1 does not represent a full calendar year of patients. This was inconsistent with the guidelines for preparing a submission to the PBAC, Version 5.0, Section 4.2, p107).

6.56 The PBAC considered that the assumptions used to estimate cabozantinib utilisation in the TKI-naïve post-immunotherapy setting and TKI use in the 'status quo' (i.e. the current use of cabozantinib, sunitinib and pazopanib) were not adequately justified and the underlying calculations were not clearly presented in the resubmission. A key assumption was that 80% of patients will receive 2L (post-TKI) therapies and 60% will receive 3L therapies. The PBAC previously considered that these uptake rates were higher than would be expected, for example it was unclear whether these rates adequately accounted for the proportion of patients who would be likely to commence another line of therapy, given that patients may become unsuitable for further lines of treatment for a variety of reasons (e.g. death, ECOG status or patient preference) (paras 6.10-6.12 and 7.4, cabozantinib, Ratified Minutes, November 2019 PBAC meeting). Further, the resubmission continued to assume that, under the status quo, a relatively high proportion of patients treated with NIVO + IPI in the first-line setting would receive cabozantinib in the third-line setting. No evidence was provided to support this assumption (i.e. that a proportion of Stage IV RCC patients (at intermediate or poor prognostic risk) would progress on NIVO+IPI, then progress on sunitinib or pazopanib, then undergo treatment with cabozantinib). This affected both the estimated increase in cabozantinib in the TKI-naïve post-immunotherapy setting and also the offsets for use of cabozantinib (and sunitinib and pazopanib) in its existing listing (i.e. the resubmission overestimated the use of TKIs under the 'status quo').

6.57 The estimated duration of cabozantinib and sunitinib in the treatment-naïve setting was not adequately justified and was inconsistent with the duration estimated in the

economic model. In some of the second-line settings, PBS 10% sample data were used to calculate the treatment duration, however the resubmission applied the median rather than mean months of treatment and therefore underestimated duration of treatment.

6.58 The estimated use and financial implications using the resubmission's estimated effective prices are presented in Table 20.

Table 20: Estimated use and financial implications – effective prices for TKI-naïve and post-TKI

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use – cabozantinib TKI-naïve (1L and 2L post-IO)						
Number of patient months treated – 1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patient months treated – 2L post-IO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated[a] – 1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated[a] – 2L post-IO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated extent of use – combined (total requested population of TKI-naïve patients)						
Number of patient months treated – Total (all TKI naïve)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated[a] – Total (all TKI naïve)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[b] – Total (all TKI naïve)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of cabozantinib – effective price						
Cost to PBS/RPBS less copayments – 1L	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments – 2L post-IO	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments – TKI naive	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated cost offsets for sunitinib, pazopanib and cabozantinib (post-TKI existing listing)						
Cost to PBS/RPBS less copayments – cabozantinib post TKI existing listing only	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments – sunitinib and pazopanib	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments – Total offsets	-$[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]
Previous submission March 2019 (cabozantinib listing only, not simultaneous listing with NIVO+IPI)– published prices						
Net cost to PBS/RPBS	$29,269,778	$35,420,184	$37,988,001	$40,700,144	$43,564,150	$46,587,935

Source: Excel spreadsheet 'Epidemiology model', sheet 'Control Panel' columns V, W and X. Excel spreadsheet 'Section 4 cost and utilisation model', sheets '3c. Impact – new (EFF)', '4a. Scripts – changed' and '4b. Impact – changed (EFF)' sheet '4c. Impact – displaced (EFF). Table 4.17, p.230 Table 4.21, p.233 of the resubmission

Abbreviations: 1L = first-line, 2L = second-line, IO = immunotherapy, TKI = tyrosine kinase inhibitor,

Note: [a] Calculated by dividing patient months by the treatment duration assumed in the financial estimates, which was 10 months for IL and 8 months for 2L post-IO.

[b] Assuming 13 per year as estimated by the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.59 The total cost to the PBS/RPBS of listing cabozantinib was estimated to be a saving of less than $10 million in Year 6, with a total cost of less than $10 million in the first 6 years of listing using the resubmission estimated effective prices. These costs were based on the published price of the comparator. The net cost to the PBS will change once the effective price of the comparator is applied.

6.60 The effective AEMP for cabozantinib in the proposed TKI-naïve settings (with or without prior immunotherapy) is lower than in the existing post-TKI setting, and the majority of the cost savings from displacement were due to the assumed substitution of cabozantinib in the second-line and subsequent settings (27% of cost offsets in Year 1, increasing to 75% of cost offsets in Year 6 using published prices). The resubmission estimated there would be a reduction in expenditure on cabozantinib under the existing post-TKI listing of $30 – $60 million over six years.

Financial Management – Risk Sharing Arrangements

6.61 The resubmission did not propose a risk-sharing arrangement (RSA).

6.62 The resubmission proposed that the existing RSA for cabozantinib post-TKI be removed. In November 2019, the PBAC considered a request from the sponsor to either change or remove the existing RSA. The PBAC did not advise a change to the existing RSA but acknowledged that the original rationale for the existing caps (which were to address the risk of sequential use of cabozantinib and NIVO monotherapy) may no longer be relevant for patients who use NIVO+IPI in the first-line setting (paragraphs 7.1-7.2, cabozantinib, PBAC Minutes, November 2019 PBAC meeting). The PSCR argued that an RSA would no longer be required as it claimed that the submission demonstrated that cabozantinib is cost-effective in the TKI-naïve setting, therefore the risk of cabozantinib use outside the existing restriction has been removed. The pre-PBAC response further argued that the rationale for the existing RSA in the post-TKI setting no longer exists.

6.63 The financial estimates include reductions in the use of cabozantinib under the existing post-TKI listing, and the cost-effectiveness relies on reduced use of subsequent therapies. The ESC considered that, given the uncertain offsets for later line use, a combined RSA may be required across the proposed and existing indications to account for both the proposed increase in eligible patients due to listing in the TKI-naïve setting (both treatment-naïve and TKI-naïve post-immunotherapy) and the expected decrease in patients in the existing post-TKI setting.

6.64 The total increase to the existing RSA if it is adjusted by the amounts assumed in the financial estimates (i.e. both an increase to account for the new TKI-naïve listing and a decrease to account for reduced use of cabozantinib under the existing listing) would result in an increase to the existing caps of less than $10 million in Year 6 and an increase of $20 – $30 million over 6 years (if the existing cap is assumed to roll over at

the value set in 2022-23). This is higher than the net cost estimated in the financial estimates, which also include the impacts on sunitinib and pazopanib use. Note these numbers are indicative only as they are based on the requested price and financial estimates proposed in the resubmission, which the PBAC considered may not be reliable.

Weighted price

6.65 The ESC considered that a combined 'line-agnostic' listing and a weighted price across the new and existing listings may be appropriate as outlined in the 'Requested listing' section. The tables below show an indicative calculation of a weighted price based on the script numbers estimated in the submission (and as such would change with any changes to the financial estimates). These are based on Years 2 to 6 given the submission calculated Year 1 as a part year.

Table 21: Script number estimates from submission: proportion of total use that will be in the new settings (calculated by ESC)

	Year 2	Year 3	Year 4	Year 5	Year 6
New listing					
Total number of scripts in new settings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Existing setting					
Current number of scripts in existing setting 'status quo'. Based on existing RSA	[redacted]	[redacted]	[redacted]	[redacted] [a]	[redacted] [a]
Reduced number of scripts in existing setting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised number of scripts in existing setting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of total use that is estimated to be in the new setting (per financial estimates in submission)					
Proportion of total use in the new settings	80%	84%	84%	85%	86%

Source: Calculated during preparation of the ESC advice using 'Section 4 cost and utilisation model' and current number of scripts in the existing setting based on the existing deed.

[a] The existing RSA expires in 2022-23. In the table above, the last 2 years have been calculated by assuming that the deed rolls over at the cap set in 2022-23.

Table 22: Calculation of a weighted price (based on script numbers from the submission and the existing RSA)

Calculation of weighted price	Proportion of use	AEMP
New setting	84% [a]	$[redacted]
Existing setting	16% [a]	$[redacted]
Weighted price (based on script numbers over 6 years)		$[redacted]

Source: Calculated during preparation of the ESC advice

[a] Proportion of use is based on total scripts across Years 2 to 6

6.66 The pre-PBAC response noted that the above calculations were based on the existing RSA for the 'status quo' (i.e. the current number of scripts in the existing setting post-TKI) which does not account for changes to the RCC treatment algorithm with the listing of NIVO+IPI. The pre-PBAC response proposed an alternative calculation of the weighted price using the resubmission's estimated 'status quo', which estimated a significantly higher number of scripts in the existing setting than are included in the existing RSA. This resulted in a higher proportion of total use being in the existing setting (34% was estimated in the pre-PBAC response versus 16% when the current RSA is used), and thus a higher weighted price ($[redacted] versus [redacted]).

6.67 However, the PBAC considered that, in addition to overestimating utilisation in the new requested settings, the resubmission had also overestimated TKI utilisation under the 'status quo' (as outlined in Paragraph 6.57). The PBAC noted that the resubmission estimated that utilisation of cabozantinib under the status quo would be significantly higher than had been agreed in the existing RSA despite the intervening changes to the treatment algorithm (i.e. the listing of NIVO+IPI) being likely to move cabozantinib from a second-line to a third-line setting for the majority of patients. As such, the PBAC re-iterated its previous view that changes to the algorithm may reduce, rather than increase, the size of the specific patient population in which cabozantinib is listed (paragraph 7.5, cabozantinib PBAC Minutes, November 2019).

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of cabozantinib for the treatment of patients with stage IV clear cell variant RCC who have not previously been treated with a TKI. The PBAC considered that the comparative clinical benefit was small and uncertain, and the incremental cost-effectiveness ratio was significantly underestimated due to the inclusion of an overall survival benefit that was not supported by the clinical evidence. The PBAC considered that the overall financial impact, including reductions in the use of cabozantinib in its existing later-line setting, were not reliably estimated in the resubmission.

7.2 The resubmission proposed separate restrictions for the existing and requested indications. However, the PBAC considered that a combined 'line-agnostic' listing for cabozantinib would more appropriately reflect the likely use of cabozantinib given the changes to the treatment algorithm, and that there was no clinical rationale for having separate listings for cabozantinib in the existing and requested settings.

7.3 The resubmission nominated sunitinib as the main comparator. The PBAC considered that sunitinib and pazopanib are the appropriate main comparators. The PBAC re-iterated that sunitinib was a reasonable proxy for pazopanib in terms of the clinical evidence presented, and noted that pazopanib has a lower effective price than sunitinib (as outlined in Section 12 of the PSD for pazopanib from March 2012).

7.4 Unchanged from the previous submission, the evidence in the treatment-naïve setting was based on the CABOSUN trial, a relatively small (n=157) Phase II open-label trial of cabozantinib versus sunitinib. The PBAC re-iterated its previous view that:

- while a statistically significant improvement in PFS was shown for cabozantinib, the magnitude was uncertain and likely overestimated as the trial had a high risk of bias due to the open-label design and substantial differences in the investigator-assessed and IRC analyses of PFS.
- the resubmission's claim that there was a trend towards improved OS was not supported by the evidence presented. The difference in OS for cabozantinib versus sunitinib was not statistically significant and appeared to be decreasing

with additional follow-up.
- an improvement in quality of life had not been adequately demonstrated.

7.5 In the TKI-naïve post-immunotherapy setting, the studies presented were small, single arm, cohort studies with limited information available about study design and patient characteristics. The studies were not designed to investigate the use of cabozantinib post-immunotherapy and did not provide comparative evidence versus sunitinib (or pazopanib). The PBAC considered that the applicability of the CABOSUN trial to the TKI-naïve post-immunotherapy setting was uncertain. The PBAC considered that, given the paucity of evidence presented, the absolute and relative benefits of cabozantinib versus sunitinib were unknown in this setting.

7.6 Overall, the PBAC considered that the clinical need for cabozantinib was limited as:

- In the treatment-naïve setting: NIVO+IPI is available and will be used in the majority of patients (the resubmission estimated that 10% of treatment-naïve patients would be treated with cabozantinib).
- In the TKI-naïve post-immunotherapy setting: While this is the setting in which cabozantinib may have the larger clinical role (the financial estimates predicted that around 75% of use under the requested listing would be in the first TKI post-immunotherapy setting), the PBAC considered that the absolute and relative benefit of cabozantinib versus sunitinib in this setting were unknown.

7.7 The PBAC considered that the resubmission had significantly underestimated the ICER per QALY as:

- an OS benefit was included that was not supported by the clinical evidence.
- the post-progression costs per cycle were higher in the sunitinib arm than in the cabozantinib arm, which the PBAC considered was inadequately supported.
- the cost-utility analysis assessed the use of cabozantinib in the treatment-naive setting only. The PBAC considered that the applicability of the economic model to the TKI-naive post-immunotherapy setting was uncertain.

Overall, the PBAC considered that the economic model did not provide a reliable basis for estimating the cost-effectiveness of cabozantinib in the requested settings.

7.8 The PBAC considered that a CMA would be appropriate given the uncertain and likely small increase in PFS, the absence of a demonstrated OS benefit or improvement in quality of life, and the uncertain applicability of the clinical data and economic model to the TKI-naive post-immunotherapy setting.

7.9 The PBAC considered that the CMA should take into account the differences in mean treatment duration with cabozantinib and sunitinib, extrapolated from the time to treatment discontinuation (TTD) results of the CABOSUN trial. The PBAC noted that the longer treatment duration with cabozantinib than with sunitinib resulted in the cost per day of cabozantinib treatment being less than the cost per day for sunitinib.

7.10 The PBAC noted that the economic model incorporated cost offsets for (a) a shorter duration of post-progression treatment and (b) a lower cost per cycle of post-progression treatment in the cabozantinib arm than in the sunitinib arm. The PBAC considered that it may be reasonable for the CMA to include some offsets for a shorter duration of post-progression treatment given the longer treatment duration with cabozantinib. However, the PBAC considered that the estimated cost per cycle of post-progression treatment was inadequately supported, and that it was not reasonable to assume a difference in the cost per cycle of post-progression treatment between the arms. The estimated duration of post-progression therapy should be based on a scenario with no difference in OS between the arms, given the PBAC considered that it was not reasonable to include an OS advantage.

7.11 The PBAC considered that any cost offsets for reduced use of treatment in the post-progression setting would need to be conservative given the aforementioned issues with clinical data (i.e. the uncertain and likely small increase in PFS, the absence of a demonstrated OS benefit, and the uncertain applicability). As the aim of the economic evaluation would be a CMA that is adjusted for the difference in treatment duration (pre- and post-progression), the PBAC considered that any revised analysis would be unlikely to support a cost per day for cabozantinib that is higher than the average cost per day for sunitinib.

7.12 The PBAC considered that the treatment-naïve eligible population was likely overestimated as patients who relapse to Stage IV from an earlier stage of RCC were double-counted in the incidence approach used, and many of the assumptions used were higher than those available elsewhere in the literature. Overall, the PBAC considered that the resubmission had significantly overestimated the utilisation of cabozantinib in the requested settings.

7.13 The resubmission estimated the use of currently-listed RCC drugs under the status quo in order to determine the offsets for reduced use of cabozantinib (in its existing listing), sunitinib and pazopanib. The PBAC considered that the assumptions underpinning these calculations were not adequately justified, and that the utilisation of TKIs under the existing listings were likely overestimated. A key issue was that the resubmission assumed that 80% of patients will receive second-line (post-TKI) therapies and 60% will receive third-line therapies. The PBAC re-iterated its previous view that these uptake rates were higher than would be expected (as outlined in paragraph 6.57).

7.14 The PBAC considered that a combined RSA would be required across the proposed and existing cabozantinib indications to ensure that the offsets in the existing later-line setting (which are required for the proposed setting to be cost-effective) are realised. The PBAC also considered that a combined treatment line-agnostic listing and a weighted price across the new and existing listings would be appropriate. The PBAC considered that the combined RSA and weighted price would need to be based on more reliable estimates of utilisation under the proposed new listings and the status

quo, as outlined in the 'Estimated PBS usage & financial implications' and 'Financial Management – Risk Sharing Arrangement' sections above.

7.15 The PBAC considered that any resubmission would need to be a major resubmission and would need to:

- be based on a combined treatment line-agnostic restriction;
- be based on a CMA versus sunitinib based on the mean duration of treatment with each drug, but acknowledging that a cost offset for a shorter duration of post-progression treatment with cabozantinib may be reasonable;
- revise the financial estimates based on patients treated rather than patient months, and addressing the overestimation of cabozantinib utilisation in the requested settings and the overestimation of the use of currently-listed RCC drugs under the status quo; and
- include a combined RSA and weighted price as outlined above.

7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.