

7.02 CABOZANTINIB, Tablet 20 mg, Tablet 40 mg, Tablet 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 who have not been previously treated with a tyrosine kinase inhibitor (TKI) (referred to as ‘the new listing’). The resubmission requested that the new listing be combined with the existing listing of cabozantinib (patients who have already received treatment with a TKI irrespective of IMDC risk classification) to form a line-agnostic restriction. The line-agnostic restriction was consistent with the previous advice from the PBAC (para 7.15, cabozantinib Public Document Summary (PSD), March 2020 PBAC Meeting).
- 1.2 Listing was requested on the basis of a cost-analysis versus sunitinib.
- 1.3 The resubmission’s PICO is presented in Table 1. In the March 2020 submission, the clinical claim was that “cabozantinib improved overall survival (OS)”, this has been changed to a claim of “similar OS” compared with sunitinib. The remainder of the PICO was unchanged from the March 2020 submission.

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 orally once daily (QD) until disease progression or unacceptable toxicity.
Comparator	Sunitinib (Sutent®), 50 mg orally QD 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	Compared to sunitinib cabozantinib provides: <ul style="list-style-type: none"> • Significantly superior PFS and ORR; • Similar OS and Different but broadly comparable safety.

Source: Table 1-21, p 7; Table 1-2, p 10; section 2.8.2, p 25 of the resubmission.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium criteria; OS = overall survival; RCC = renal cell carcinoma; TKI = Tyrosine-kinase inhibitor.

Note: Blue shading denotes text remains unchanged from the previous resubmission.

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 2020 meeting for use in patients with stage IV clear cell variant RCC who have not previously been treated with a TKI on the basis that the comparative clinical benefit was small and uncertain, and the incremental cost-effectiveness ratio (ICER) 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 setting (post-TKI), was not reliably estimated in the resubmission (para 7.1, cabozantinib PSD, March 2020 PBAC meeting). A summary of the key matters of concern from the March 2020 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 it was addressed in the resubmission
Economic evaluation: CMA	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-naïve post-immunotherapy setting (para 7.8, March 2020 PSD).	Addressed. The resubmission relied on the same clinical evidence as presented in March 2020. The resubmission referred to the economic analysis as a 'CMA', however it relied upon a difference in PFS and associated differences in treatment duration and time on post-progression therapy and thus may be better classified as a cost-analysis. The approach to the analysis was consistent with that recommended by the PBAC in March 2020.
Economic evaluation: CMA, duration of treatment	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 (para 7.9, March 2020 PSD).	Addressed. Mean TTD from the economic model included in the March 2020 resubmission was used. The extrapolated outcome appears appropriate.

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Component	Matter of concern	How it was addressed in the resubmission
Economic evaluation: cost-offsets, post-progression costs	<p>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.</p> <p>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.</p> <p>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 (para 7.10, March 2020 PSD).</p>	<p>Addressed. The resubmission applied a shorter duration of post-progression treatment for cabozantinib that was based on no difference in OS between cabozantinib and sunitinib. The cost per cycle of post-progression treatment was equivalent across the arms.</p>
Financial estimates: eligible population	<p>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 (para 7.12, March 2020 PSD).</p>	<p>Inadequately addressed. The resubmission maintained the approach used to estimate the treatment-naïve eligible population. The utilisation of cabozantinib was likely overestimated.</p>
Financial estimates: proportion patients progressing to 2L and 3L	<p>The PBAC considered that the assumptions underpinning the financial calculations were not adequately justified, and that the utilisation of TKIs under the existing listings was 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 (para 6.56 and 7.13, March 2020 PSD).</p>	<p>Not addressed. The resubmission provided new evidence (the KRAB report) to support the assumptions used, but the calculations remained overestimated.</p>
Financial estimates: RSA	<p>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 (para 7.14, March 2020 PSD).</p>	<p>Inadequately addressed. The new RSA was proposed based on the line-agnostic restriction. However, it appears to be based on unreliable estimates of utilisation in all settings.</p>

Source: Compiled during the evaluation using 7.02 cabozantinib March 2020 Public Summary Document.

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Abbreviations: CMA = cost-minimisation analysis; ESC = Economics Sub-Committee; KRAB = Kidney Cancer Australian Registry and Biobank; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression-free survival; PSD = Public Summary Document; RCC = renal cell carcinoma; RSA = Risk Sharing Agreement; TKI = tyrosine kinase inhibitor; TOT = Time-on-treatment; TTD = time-to-treatment discontinuation.

3 Requested listing

3.1 The resubmission requested a line-agnostic restriction, comprising use in patients who have not been previously treated with a TKI (with intermediate to poor risk according to the IMDC criteria) and patients who have already received treatment with a TKI irrespective of IMDC risk classification, as outlined below.

Name, restriction, manner of administration, form	Max qty (packs)	Max qty (units)	Published and Effective prices AEMP and DPMQ		Proprietary name and manufacturer
CABOZANTINIB Cabozantinib, 60 mg tablet, 30 Cabozantinib, 40 mg tablet, 30 Cabozantinib, 20 mg tablet, 30	1 1 1	30 30 30	Published AEMP \$9,800.00 Published DPMQ \$9,976.96	Effective AEMP \$ [REDACTED] ^a Effective DPMQ \$ [REDACTED] ^a	Cabometyx® Ipser Pty Ltd
Category / Program	General Schedule/Section 85				
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)				
Treatment phase:	Initial				
Restriction:	Authority Required (STREAMLINED)				
Clinical criteria:	The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), OR Patient must have progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) following prior treatment with a tyrosine kinase inhibitor, AND Patient must have a WHO performance status of 2 or less, AND The treatment must be the sole PBS-subsidised therapy for this condition.				
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions Stable disease (SD) is small changes that do not meet above criteria. Patients who have developed intolerance to sunitinib or pazopanib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised cabozantinib.				

Source: Table 1.5, p.20 of the resubmission.

^a Per Pre-PBAC response, p4

Abbreviations: CR = complete response; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PBS = Pharmaceutical Benefits Scheme; PD = progressive disease; PR = partial response; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria In Solid Tumours; SD = stable disease; WHO = World Health Organization

Note: Blue shading denotes text remains unchanged from the previous resubmission.

Category / Program	General Schedule/Section 85
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuing treatment
Restriction:	Authority Required (STREAMLINED)
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND</p> <p>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition AND</p> <p>Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p> <p>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions Stable disease (SD) is small changes that do not meet above criteria.</p>

Source: Table 1.6, p.21 of the resubmission.

Abbreviations: CR = complete response; PBS = Pharmaceutical Benefits Scheme; PD = progressive disease; PR = partial response; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria In Solid Tumours; SD = stable disease

Note: Blue shading denotes text remains unchanged from the previous resubmission.

3.2 The resubmission requested a special pricing arrangement with an effective approved ex-manufacturer price (AEMP) of \$ [REDACTED] for all three strengths, which was revised to \$ [REDACTED] in the pre-PBAC response. The pre-PBAC response's requested price was the result of weighting: the proposed new listing price obtained from the cost-analysis versus sunitinib (\$ [REDACTED]; [REDACTED] %); and the existing listing price (\$ [REDACTED]; [REDACTED] %). The cost-analysis price is 16% lower than the price proposed in the March 2020 resubmission (\$ [REDACTED]) for use in the TKI-naïve and post-immunotherapy setting (first-line).

3.3 The resubmission's restriction proposed use in patients who have:

- intermediate or poor risk according to IMDC criteria – which is the new requested listing and allows use in patients who are either treatment-naïve or TKI-naïve post-immunotherapy. This would allow cabozantinib to be used in treatment-naïve patients (e.g. who are unsuitable for immunotherapy), or as the first TKI in patients previously treated with immunotherapy such as nivolumab and ipilimumab (hereafter referred to as NIVO+IPI). The addition of this criterion is the key change compared with the existing listing; or
- progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) following prior treatment with a tyrosine kinase inhibitor (TKI) – which is the existing listing.

As such, the restriction proposed by the sponsor would exclude use in patients with favourable risk who are TKI-naïve post-immunotherapy. The PBAC considered that it

may be simpler to state this ‘excluded group’ in the restriction, rather than outlining the two aforementioned groups i.e. include a criterion:

- The treatment must not be prescribed for a patient with favourable risk disease (IMDC score of 0) prior to use of any of: (i) pazopanib, (ii) sunitinib.
- 3.4 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”. However, the PBAC reiterated its March 2020 consideration that this would not be appropriate to include given the likelihood of patients who have developed an intolerance to a prior TKI also having tolerability issues with cabozantinib (para 3.7, cabozantinib PSD, March 2020 PBAC meeting).
- 3.5 The sunitinib restriction does not allow use in patients who have progressed on pazopanib (and vice versa). Similarly, the PBAC considered that sunitinib and/or pazopanib should not be used following progression on cabozantinib, i.e. the sunitinib and pazopanib restrictions should be updated to state:
- PBS-subsidy does not apply to a patient who has progressive disease whilst on, or, who has recurrent disease following treatment with any of: (i) cabozantinib, (ii) pazopanib, (iii) sunitinib.

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 in 2018 representing 2.6% of all new cancer cases, with 1,069 deaths associated with this tumour type (Cancer Australia 2018; para 4.2, cabozantinib PSD, March 2019 PBAC meeting).
- 4.2 Cabozantinib is a TKI. The resubmission proposed that cabozantinib would be used as the first TKI, irrespective of prior immunotherapy exposure, in patients with intermediate to poor risk disease.

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

5 Comparator

- 5.1 The submission nominated sunitinib as the main comparator.
- 5.2 The PBAC considered sunitinib to be the appropriate comparator accepting that treatment with cabozantinib results in an improvement in PFS compared with sunitinib, and by extension pazopanib.

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 an individual and an organisation (the Medical Oncology Group of Australia (MOGA)) via the Consumer Comments facility on the PBS website. MOGA expressed its strong support for the cabozantinib resubmission, categorising it as one of the therapies of “high 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

6.3 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 2020 resubmission.

6.4 The resubmission also presented clinical evidence for cabozantinib used as the first TKI post-immunotherapy. There were six studies identified as evidence for cabozantinib as the first TKI post-immunotherapy 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). This was unchanged from the March 2020 resubmission.

6.5 Details of the included studies are provided in Table 3. No other potentially relevant studies were identified 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]

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)	<p>Clinical study report (CSR).</p> <p>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."</p> <p>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</p> <p>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."</p>	<p>31 July 2017</p> <p>Annals of oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO 2016. Denmark. 27</p> <p>J Clin Oncol 35 (6): 591-597</p> <p>European J Cancer 94:115-125.</p>
TKI-naïve post-immunotherapy		
MD Anderson CC	<p>(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.</p> <p>(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)."</p>	<p>Eur J Cancer 114:67-75.</p> <p>J Clin Oncol 36 (no.6_suppl (February 20 2018)):682-682. Poster at ASCO 2018.</p>
DFCI 1	<p>(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)."</p> <p>(Lalani et al. 2019) "Activity of cabozantinib after PD-1/PD-L1 immune checkpoint blockade in metastatic clear-cell renal cell carcinoma."</p>	<p>European Society for Medical Oncology website, accessed 2/4/19. Poster at ESMO 2018.</p> <p>Canadian Urological Association Journal 13 (2 Supplement 2):S13. Poster at CUOS 2019.</p>
Taussig / Barts	<p>(Barata, A, et al. 2018) "The efficacy of VEGFR TKI therapy after progression on immune combination therapy in metastatic renal cell carcinoma."</p> <p>(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."</p> <p>(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."</p>	<p>Br J Cancer 119:160-163.</p> <p>Journal of Clinical Oncology 36 (6 Supplement 1). Poster at ASCO 2018.</p> <p>Kidney Cancer 2 (Supplement 1):S10-S11. Poster – 16th International Kidney Cancer Symposium 2017</p>
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.

Trial ID Other ID	Protocol title/ Publication title	Publication citation
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 March 2020 resubmission.

Note: Blue shading denotes text remains unchanged from the previous resubmission.

6.6 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 IMDC 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 March 2020 resubmission

Abbreviations: AE = adverse event; IMDC = 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.

Note: Blue shading denotes text remains unchanged from the previous resubmission.

Comparative effectiveness

Treatment-naive therapy

- 6.7 Results for key clinical outcomes including PFS, OS, objective response rate (ORR), and safety from CABOSUN were unchanged from the March 2020 resubmission.
- 6.8 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 Independent Radiographical Committee (IRC) assessed PFS and 0.66 (95% CI: 0.46, 0.95) for investigator-assessed PFS. The PBAC previously considered that CABOSUN showed a statistically significant improvement in PFS for cabozantinib, but that the magnitude of benefit was uncertain and likely overestimated as the trial had a high risk of bias due to the open-label design, imbalances in missing data and with substantial differences in the investigator-assessed and IRC analyses of PFS (para 7.5, cabozantinib PSD, March 2019 PBAC meeting).

Table 5: Results of progression-free survival - CABOSUN

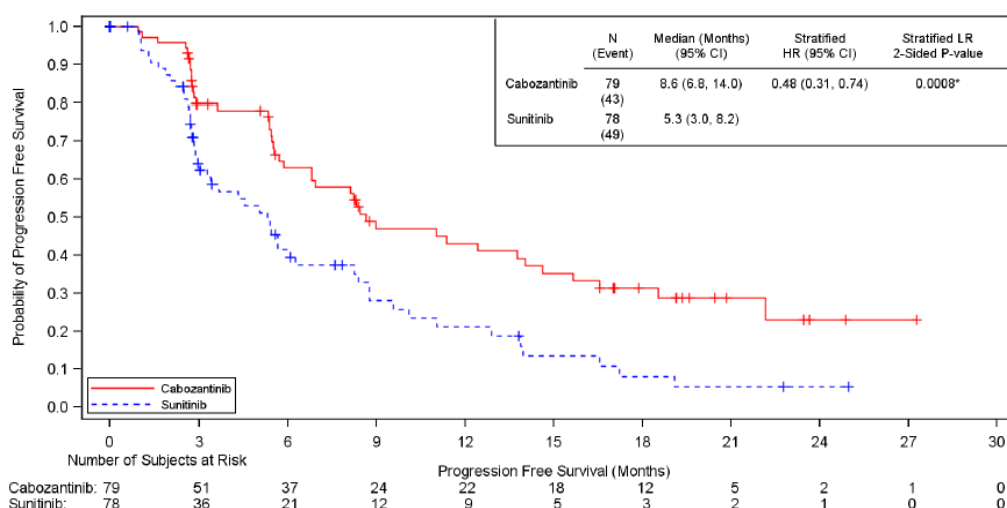
	Cabozantinib		Sunitinib		Difference in median, mths	p value ^a	HR (95% CI)
	n/N (%)	Median mths (95% CI)	n/N (%)	Median mths (95% CI)			
IRC assessed-September 2016 data-cut-off.	43/79 (54)	8.6 (6.8, 14.0)	49/78 (63)	5.3 (3.0, 8.2)	3.3	0.00	0.48 (0.31, 0.74)
Investigator assessed-April 2016 data cut-off.	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 the 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. Blue shading denotes text remains unchanged from the previous resubmission.

Figure 1: 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.

Note: Blue shading denotes text remains unchanged from the previous resubmission.

6.9 The OS results from CABOSUN are presented 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). 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 PBAC concluded 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).

Table 6: Results of overall survival - CABOSUN

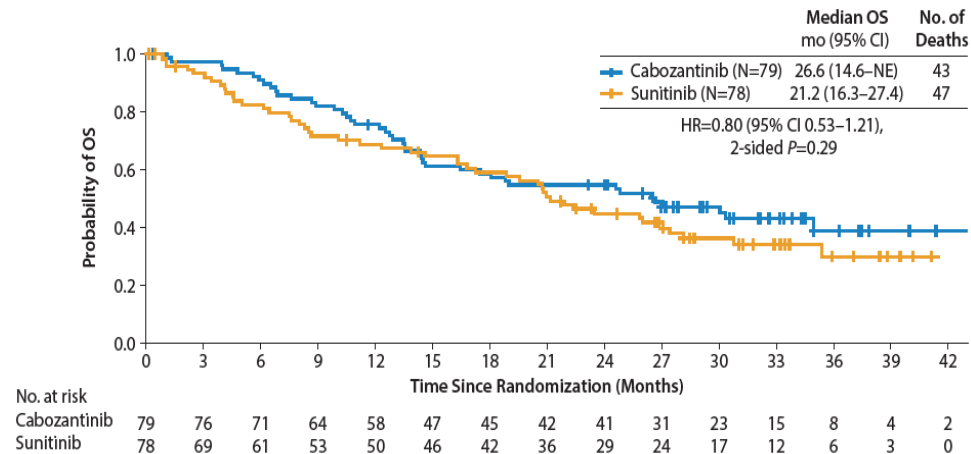
	Cabozantinib		Sunitinib		Difference in median, mths	p value ^a	HR (95% CI)
	n/N with event (%)	Median mths (95% CI)	n/N with event (%)	Median mths (95% CI)			
September 2016 cut-off.	38/79 (48)	30.3 (14.6, NE)	45/78 (58)	21.0 (16.3, 27.0)	9.3	0.17	0.74 (0.47, 1.14)
July 2017 cut-off.	43/79 (54)	26.6 (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; mths = months; n = number of participants with event; N = total participants in group; NE = not estimable.

Notes: ^aLog-rank p-value (stratified). Blue shading denotes text remains unchanged from the previous resubmission.

Figure 2: Kaplan-Meier plot of OS in CABOSUN (July 2017; ITT population)



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

Note: Blue shading denotes text remains unchanged from the previous resubmission.

TKI-naïve post-immunotherapy

6.10 Results for the clinical outcomes including PFS and OS from the studies included as clinical evidence for cabozantinib used as the first TKI post-immunotherapy and as the second (or subsequent) TKI post-immunotherapy were unchanged from the March 2020 resubmission.

6.11 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-naïve 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 al. 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 March 2020 resubmission; Table 2.11, p.23; Table 2.12, p.24 of Attachment 3 of the March 2020 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; Blue shading denotes text remains unchanged from the previous resubmission.

6.12 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-naïve 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 al. 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 March 2020 resubmission; Table 2.20, p.34; Table 2.20, p.34 of Attachment 3 of the March 2020 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; Blue shading denotes text remains unchanged from the previous resubmission.

Comparative harms

6.13 No new data on comparative harms were provided in the resubmission. 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).

Benefits/harms

6.14 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.

Clinical claim

6.15 For patients who are naïve to treatment with a TKI irrespective of prior treatment with immunotherapy, the resubmission maintained the clinical claim of superior efficacy for PFS and ORR and comparable safety relative to sunitinib (unchanged from the March 2020 resubmission). However, the resubmission changed the clinical claim for OS outcomes to be that OS outcomes for cabozantinib are similar to sunitinib.

6.16 In the first TKI post-immunotherapy setting, the resubmission described cabozantinib as significantly superior in PFS and ORR, with a similar OS to sunitinib (i.e. the same

clinical claim as in the treatment-naïve setting). The resubmission acknowledged the PBAC's view 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 treatment naïve setting" (para 6.30, cabozantinib PSD, March 2020 PBAC meeting). The resubmission stated that as there is equally limited prospective evidence for the other available TKIs in this setting, cabozantinib was assumed to be equivalent to sunitinib, with a different but broadly comparable safety profile.

- 6.17 The PBAC considered that the clinical claim of superior efficacy for PFS was adequately supported by the evidence presented but considered the magnitude was uncertain and likely overestimated. The PBAC considered that cabozantinib was non-inferior to sunitinib in terms of overall survival.
- 6.18 The PBAC considered that the claim of non-inferior (different but broadly comparable) comparative safety was reasonable.

Economic analysis

- 6.19 The resubmission presented a cost-analysis comparing cabozantinib with sunitinib. This differed from the March 2020 resubmission in which a cost-utility analysis was presented. The resubmission referred to the economic analysis as a cost-minimisation analysis (CMA), however it relied on a difference in PFS and associated differences in treatment duration and time on post-progression therapy. Thus the type of analysis may be better classified as a cost-analysis. The use of a cost-analysis was consistent with the PBAC's advice 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-naïve post-immunotherapy setting" (para 7.8, cabozantinib PSD, March 2020 PBAC Meeting). The key components of the analysis as presented in the resubmission are summarised in Table 9.

Table 9: Key components and assumptions of the cost-analysis

Component	Description
Therapeutic claim: effectiveness	Non-inferior with respect to OS
Therapeutic claim: safety	Non-inferior
Evidence base	CABOSUN
Equi-effective doses	Average dose from CABOSUN: cabozantinib 49.4 mg is equivalent to 43.7 mg sunitinib.
Mean duration of treatment*	Inputs depend on the estimates of mean duration from the economic model contained in the March 2020 resubmission: TOT: Cabozantinib 12.6 months, sunitinib 7.2 months (PFS but not on treatment: Cabozantinib 3.8 months, sunitinib 1.5 months) Post progression TOT: Cabozantinib 16.8 months, sunitinib 24.5 months OS: 33.2 months for both drugs based on OS for sunitinib
Direct medicine costs	Drug costs (sunitinib and cabozantinib)
Other costs or cost offsets	Post-progression of \$2,470 per cycle (6.49, cabozantinib PSD, March 2020 PBAC Meeting) regardless of treatment group. This was based on the resubmission's estimates of the effective price of therapies used post-progression.

Source: Table 3-1, p26 of the resubmission; compiled during the evaluation

Abbreviations: AEMP = approved ex-manufacturer price; ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium criteria; RCC = renal cell carcinoma; TKI = Tyrosine-kinase inhibitor; TOT = time on treatment

* Note that the mean duration of treatment was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.20 The resubmission estimated that using cabozantinib 49.4 mg daily for 12.6 months² was equivalent to 43.7 mg daily (4 of 6-week treatment cycle) sunitinib for 7.2 months² in achieving a similar OS outcome (33.2 months based on OS for sunitinib). The average daily doses were based on the CABOSUN trial. The duration of treatment was based on the extrapolated time on treatment (TOT) estimates from the economic model presented in the March 2020 resubmission over a time horizon of 7.5 years based on the CABOSUN data. Use of the extrapolated data from the economic model addressed the PBAC's previous advice regarding the comparison of time on treatment (paras 7.9 and 7.12, cabozantinib PSD, March 2020 PBAC meeting).
- 6.21 The duration of treatment was based on time on treatment (extrapolated from trial data), which was shorter than PFS. The period of time in which patients were assumed to be progression-free but not on any treatment (i.e. the difference between PFS and time on treatment) was longer in the cabozantinib arm than the sunitinib arm (3.8 months² versus 1.5 months²). While data on time to next treatment following treatment cessation were not provided in the submission, the evaluation considered this approach was reasonable as both PFS and time on treatment were extrapolated from the CABOSUN trial.
- 6.22 The resubmission applied cost offsets based on a shorter duration of post-progression treatment for cabozantinib (16.8 months²) than sunitinib (24.5 months²), reflecting

² Note that the mean duration of treatment was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

that cabozantinib-treated patients spend longer in the progression free period than sunitinib patients. This approach assumes a superior PFS outcome for cabozantinib compared with sunitinib, within the envelope of the same OS outcome. This was consistent with the clinical evidence presented and the PBAC's previous view that there was no difference in OS outcomes (7.4, cabozantinib PSD, March 2020 PBAC meeting).

- 6.23 The resubmission applied a cost per cycle for post-progression treatment of \$2,470, which was consistent with the ESC's preferred scenario at the March 2020 meeting (para 6.49, cabozantinib PSD, March 2020 PBAC meeting). The resubmission did not provide any additional justification for the choice of the cost of post-progression therapy, even though the PBAC previously considered that these costs were inadequately justified (para 7.10, cabozantinib PSD, March 2020 PBAC Meeting).
- 6.24 The estimated total post-progression costs reflect treatment in the TKI-naïve setting (as per CABOSUN). The evaluation considered that the use of post-progression therapy in the post-IO setting is unclear and may be of a different duration than in the TKI-naïve setting.
- 6.25 The resubmission requested that the listing of cabozantinib be considered under the pricing arrangements outlined in Clause 5.7 of the Department of Health and Medicines Australia Strategic Agreement. Specifically, the resubmission requested a price adjustment for cabozantinib, where the statutory price reductions that have been applied to the proposed comparator, sunitinib (of 5% at 5 years and 10% at 10 years), are not used to calculate the price of cabozantinib. The resubmission applied the 'pre-statutory price reduction' comparator price in the base case. Clause 5.7 is only applicable where a drug in F1 is listed on a cost-minimisation basis with a medicine on the F1 formulary. The application of Clause 5.7 of the Strategic Agreement is determined by the Minister (or Delegate), and is not a matter for the PBAC.
- 6.26 During evaluation, a number of issues were noted with the cost-analysis calculation:
- In applying post-progression costs, the resubmission did not adjust for the proportion of patients who received therapy following progression. This effectively assumed that all patients who progressed received subsequent therapy, whereas the evaluation noted that 85% of patients in CABOSUN (the pivotal trial) were treated post-progression.
 - The post-progression cost per cycle in the sunitinib arm was divided by the number of days per month (30.44), rather than by the cycle length (28 days).

The Pre-Sub-Committee-Response (PSCR) stated that it reviewed the methodological adjustments and concurred with the changes, and the pre-PBAC response appeared to incorporate these changes. The pre-PBAC response quoted an AEMP of \$ [REDACTED], equivalent to \$ [REDACTED] per day, compared to a cost per day (at the AEMP level) for sunitinib of \$ [REDACTED].

6.27 The cost-analysis inputs are presented in Table 10.

Table 10: Cost-analysis inputs

Component	Cabozantinib	Sunitinib
Medicine costs		
Average dose (per day that treatment is actually received)	49.4 mg	43.7 mg
Cost per day	-	Cost for 28 days divided by 42 to account for regime of 4 weeks on, 2 weeks off
Treatment duration*	383.20 days (12.6 months)	220.50 days (7.2 months)
Cost offsets		
Post-progression cost per 28-days	\$2,470.00	\$2,470.00
Post-progression treatment duration*	16.8 months	24.5 months
Proportion of patients requiring post-progression therapy	85%	85%

Source: Table 3-2, p29 of the resubmission; Section 3 - Economic model (Cabozantinib vs Sunitinib) - (CMA)

Note: the first two rows (average dose and cost per day) are used to calculate the 'cost per day'.

*Note that the mean duration of treatment was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.28 The PBAC noted that there were uncertainties regarding the proportion of patients who require post-progression treatment and the cost of post-progression treatment, but overall accepted that the analysis adequately demonstrated that cabozantinib is cost-effective if the cost per day for cabozantinib that is no higher than the average cost per day for sunitinib.

Drug cost/patient/course \$ [REDACTED] (using price proposed in pre-PBAC response)

6.29 The average time on treatment estimated from the model presented in the March 2020 resubmission was 12.6 months³ for cabozantinib and 7.2 months³ for sunitinib. Based on the resubmission's estimates, the drug cost/patient/course for cabozantinib was estimated to be \$ [REDACTED] (using the indication-specific price). The drug cost per patient are summarised in Table 11. The drug costs for cabozantinib are based on the price proposed in the pre-PBAC response.

³ Note that the mean duration of treatment was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 11: Drug cost per patient for cabozantinib and sunitinib

	Cabozantinib			Sunitinib		
	Trial dose and duration	Cost-analysis	Financial estimate	Trial dose and duration	Cost-analysis	Financial estimates
Mean dose (mg/day)	49.4	49.4	42.0	43.7	43.7	36.6
Mean duration (months)*	9.4 ^b	12.6	13.0	5.7 ^b	7.2	7.0
Cost per patient for 30-day supply (cabozantinib) and 28-day supply (sunitinib)	\$ [REDACTED] (weighted price)	\$ [REDACTED] (indication-specific)	\$ [REDACTED] (weighted price)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED] ^a
Adjustments to drug cost	Treatment interruption: 2.67%	-	-	Treatment interruptions: 0.06%	-	
				Dosing schedule: 4 weeks on, 2 weeks off every 6 weeks		
Adjusted cost/patient/month	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost/patient/course	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Developed during the evaluation

Note: ^a This was obtained from the expected dose based on number of different packs of sunitinib in Year 1-6 from the financial model of the resubmission. The mean dose per day in the financial estimates was 36.5 mg which resulted in the cost of \$ [REDACTED] per 28-day supply.

^b Truncated means from CABOSUN

* Note that the mean duration of treatment was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.30 The cabozantinib cost per patient in the cost-analysis was an indication-specific price for the first-line setting, which was lower than the weighted price proposed across the whole line-agnostic listing. This resulted in a lower cost per patient in the economic analysis compared with the financial estimates for cabozantinib. The higher cost of sunitinib in the economic model compared to the financial estimates was due to the application of Clause 5.7 in the model.

Estimated PBS usage & financial implications

6.31 This resubmission was not considered by DUSC. The resubmission used a mixed epidemiological and market share approach.

6.32 As part of estimating the combined utilisation across the TKI naïve (new) and post-TKI (existing) listings, the resubmission re-estimated the utilisation of cabozantinib in the post-TKI setting, which was referred to as the 'status quo' (i.e. the resubmission re-estimated the use of cabozantinib, sunitinib, and pazopanib assuming no change to the current cabozantinib post-TKI listing). The resubmission's re-estimates of the status quo led to higher estimates of the current utilisation of cabozantinib than have been agreed under the current RSA. The ESC noted that these high 'status quo' estimates were then used as a basis to estimate the utilisation of cabozantinib for the proposed new listing i.e. the use of cabozantinib in TKI-naïve patients (i.e. first-line treatment-naïve patients and second-line patients following NIVO+IPI), and also to estimate the impact on use in patients following a TKI (i.e. second-line patients following a first-line TKI, and third-line patients following NIVO+IPI as well as a TKI). The ESC reiterated the PBAC's previous consideration that changes to the treatment algorithm (e.g. the listing of NIVO+IPI in the first-line setting) may reduce, rather than

increase, the size of the specific patient population in which cabozantinib is currently listed (paragraphs 7.2 and 7.5, cabozantinib PBAC Minutes, November 2019). The pre-PBAC response adjusted a number of parameters in the financial estimates, which resulted in closer alignment of the ‘status quo’ cabozantinib script numbers (i.e. utilisation assuming no change to the current post-TKI listing) and those agreed for cabozantinib post-TKI use under the existing RSA.

6.33 The data sources used to estimate the expected use of cabozantinib are summarised in Table 12, and are largely unchanged compared with the previous submission.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible patients		
Treatment-naïve eligible population	14.2 per 100,000 kidney cancer incidences; AIHW and National Mortality Database; of these, 90% is RCC; unsourced; of RCC, 30% is Stage IV; unsourced; 23% of early stage progresses to Stage IV.	The ESC considered this was likely overestimated per the PBAC’s previous comments (7.12, cabozantinib PSD, March 2020 PBAC Meeting). The pre-PBAC response’s revisions to the number of treated 1L patients addressed this issue.
Number treated 1L patients	76% of the treatment-naïve eligible population i.e. Year 1: 1,183 increasing to 1,276 in Year 6. The resubmission stated that the 76% was estimated based on the DUSC data. The pre-PBAC response revised this to: Year 1: 1,043 increasing by 4.2% per year, based on DUSC data	The ESC considered the resubmission’s estimates were likely overestimated, noting they were higher than estimated from the DUSC data (973 in 2018, 961 in 2019, and 937 from Q1 2019 to Q1 2020; after listing NIVO+IPI). To address this, the pre-PBAC response based the number of patients treated on the DUSC data, increasing by 4.2% per year based on growth in the number of patients initiating PBS 1L RCC treatment.
Duration of treatment (months)		
TKI-naïve cabozantinib	13; Mean TOT of cabozantinib of the economic model from the March 2020 resubmission.	Reasonable
TKI-naïve post-IO cabozantinib	13; Mean TOT of cabozantinib (i.e. TKI-naïve) of the economic model from the March 2020 resubmission. Adjusted to 12 months in the pre-PBAC response.	The ESC considered 13 months might be overly long given that patients already had 16 months of treatment with NIVO+IPI (see below for NIVO+IPI duration of treatment).
Post-TKI cabozantinib	9; PBS 10% sample	Reasonable
Post-IO & TKI cabozantinib	9; PBS 10% sample; Adjusted to 8 months in the pre-PBAC response	The ESC considered 9 months might be overly long given that patients already had 16 and 7 months of treatment with NIVO+IPI and sunitinib/pazopanib respectively.
NIVO+IPI	16; Calculated from the average number of treatment cycles of NIVO+IPI reported in PSD (Nov. PBAC 2017). 30% assumed to discontinue after 2 months of treatment.	
TKI-naïve sunitinib/pazopanib	7; Mean TOT of sunitinib in the economic model from the March 2020 resubmission.	Reasonable
Post-IO sunitinib/pazopanib	7; Mean TOT of sunitinib in the economic model from the March 2020 resubmission. Adjusted to 6 months in the pre-PBAC response.	Inadequately justified

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Parameter	Value applied and source	Comment
Market share: 1L		
Cabozantinib	10%; Assumption that cabozantinib will take all intermediate to poor risk patients who are IO-inappropriate: 10%	The ESC considered this appeared low in comparison to the assumed 57% market share for sunitinib/pazopanib, and was inadequately justified.
NIVO+IPI	33%; Based on DUSC data from 2019.	The ESC and PBAC considered this appeared low. NIVO+IPI was only listed on 1 March 2019. Would increase to 38% if the first quarter of 2019 was excluded. The PBAC considered that the low market share likely reflects its recent listing, and that usage would likely increase over time.
Sunitinib/pazopanib	57%. The rest of the 1L market share	The ESC and PBAC considered this appeared implausibly high compared with 10% market share of cabozantinib in this setting, reflecting the potential underestimation of NIVO+IPI use. Inadequately justified by the resubmission. Significantly higher than in the previous submission where all patients who were intermediate-to-poor risk who were unsuitable for immunotherapy were assumed to receive cabozantinib.
Market share: Post-IO		
Cabozantinib	50%; Assumption that cabozantinib will substitute current use of sunitinib/pazopanib post-IO	Inadequately justified
Sunitinib/pazopanib	50% (70%/30%); Assumption based on the opinions expressed within sponsor's advisory board meeting.	
Market share: Post-TKI i.e. in the resubmission post sunitinib/pazopanib		
Cabozantinib	40%; Assumption. The █% of post-TKI market was the agreed cap for cabozantinib post-TKI RSA (7.11, cabozantinib PSD, December 2017 PBAC Meeting)	The ESC considered this was likely overestimated. The economic model in the previous submission assumed that 16% of patients received cabozantinib after TKI (sunitinib) (Table 14, cabozantinib PSD, March 2020 PBAC Meeting), though a number of issues were identified with this approach.
Market share: Post-IO & TKI i.e. in the resubmission post NIVO+IPI, then sunitinib/pazopanib		
Cabozantinib	90%; 10% PBS analysis of patients receiving NIVO+IPI. Adjusted to 58% in the pre-PBAC response.	The ESC considered 90% was likely overestimated and inadequately supported by evidence. Several treatments are PBS listed for this setting. Overestimating this parameter increases the weighted price.
Progressed patients		
1L patients who progress to 2L	77%; KRAB report. Aligns with the assumed 85% of patients who were treated in the first line setting receiving a second-line treatment (assumptions used to derive the nivolumab monotherapy RSA, per the RCC March 2017 PSD for nivolumab, paragraph 6.47).	The ESC and PBAC considered this remained overly high and remained largely unchanged compared with the March 2020 resubmission (80%). KRAB report may lack applicability e.g. 11% received NIVO+IPI 1L (using data commencing Jan 2017), versus 33% in the DUSC data.
2L patients who progress to 3L	64%; KRAB report	The ESC and PBAC considered this remained overly high compared with the March 2020 resubmission (60%). Likely overestimated per comment above.

Source: Developed based on Table 4-1 p31; Table 4-2 p35; Table 4-9 p43; Table 4-10 p43; Attachment 4 - Epidemiology model.xlsx; Section 4 cost and utilisation model.xlsx

Abbreviations: 1L = first-line; 2L = second-line; 3L = third-line; ABS = Australian Bureau of Statistics; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; DUSC = Drug Utilisation Sub Committee; IO = immunotherapy; KRAB = Kidney Cancer Australian Registry and Biobank; MBS = Medicare Benefits Scheme; NIVO+IPI = nivolumab+ipilimumab; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; PSD = Public Summary Document; RCC = renal cell carcinoma; RPBS = Repatriation Pharmaceutical Benefits Scheme; RSA = Risk Sharing Agreement; TKI = tyrosine kinase inhibitor; TOT = time on treatment

6.34 The ESC considered the use of all treatments was likely substantially overestimated due to:

- the number of patients starting first-line treatment was overestimated. The resubmission continued to apply assumptions in the financial estimates which the PBAC had noted were likely to result in an overestimate of the treated population including: the proportion of patients with RCC and the proportion diagnosed with stage IV disease were higher than those available elsewhere in the literature; and that assuming 23% of early stage patients progress to stage IV results in double-counted patients (Table 19 and para 6.54, cabozantinib PSD, March 2020 PBAC Meeting). The ESC further considered that the approach used to estimate the TKI-naïve eligible population appeared unnecessarily complex given that data estimating the number of patients starting RCC treatment had already been provided by the DUSC Secretariat. To address this, the pre-PBAC response adjusted its estimate of the number of patients starting first-line treatment to be based the data provided by the DUSC Secretariat. The pre-PBAC response applied a growth rate of 4.2% per year based on growth in the number of patients initiating PBS-subsidised first-line RCC treatment. The PBAC considered this was reasonable.
- the likely overestimated proportions of patients receiving second-line and third-line treatment. The resubmission assumed that 77% of patients receiving first-line treatment will receive second-line treatment and 64% of patients receiving second-line treatment will receive third-line treatment based on the Kidney Cancer Australian Registry and Biobank (KRAB) report. The applicability of the KRAB report to the PBS setting was unclear. In particular, the report included retrospective data from 1 January 2017 which was prior to the listing of NIVO+IPI on 1 March 2019. While the resubmission assumed that 33% of patients receive NIVO+IPI as first-line treatment (based on data from the DUSC), only 11% of patients received NIVO+IPI as first-line treatment in the KRAB report. If a higher proportion of patients receive NIVO+IPI (as assumed by the resubmission), a lower proportion would be expected to progress to second-line treatment than in the KRAB report given the higher efficacy of NIVO+IPI compared with other drugs used in the first-line setting. Overall, the ESC and the PBAC considered that the application of these estimates from the KRAB report likely overestimated the number of patients progressing to later-line cabozantinib. The estimates of 77% and 64% were very similar to those applied in the March 2020 resubmission (80% and 64% in second and third-line, respectively), which the PBAC previously

identified as being uncertain and resulting in overestimates of use. The PBAC agreed with the ESC that these proportions were overestimated.

- 6.35 The ESC considered that the use of cabozantinib post-TKI, both for the status quo and new listing scenario, was likely further overestimated, in particular due to overestimating the market share of cabozantinib post-IO and post-TKI (90%). There was no evidence for such high use of cabozantinib in this setting. To address this, the pre-PBAC response adjusted the proportion of patients receiving cabozantinib in the post-IO and post-TKI (third-line) setting from 90% to 58%. No basis was provided for the revised figure, though the pre-PBAC response argued that a high market share was selected on the basis of superior clinical data from METEOR, compared to the remaining treatment options available for patients (i.e. axitinib, everolimus or sorafenib).
- 6.36 The ESC noted the proportion of use of cabozantinib in the (lower priced) TKI-naïve setting was likely underestimated (although not the number of scripts for the reasons outlined above) due to the following assumptions regarding market share:
- first-line treatment-naïve patients: 10% market share for cabozantinib. This appears low in comparison to the assumed 57% market share for sunitinib/pazopanib. The ESC and PBAC considered that the resubmission's estimate that sunitinib/pazopanib would have a 57% share of the first-line (treatment-naïve) market was implausibly high and reflected the potential underestimation of NIVO+IPI use. The estimate of 57% was significantly higher than in the previous submission where all patients who were intermediate-to-poor risk who were unsuitable for immunotherapy were assumed to receive cabozantinib.
 - second-line following NIVO+IPI: 33% market share for first-line NIVO+IPI. The ESC and PBAC considered that the market share of NIVO+IPI was underestimated as the DUSC utilisation data likely reflects its recent listing, which will likely increase over time. Underestimating the first-line use of NIVO+IPI results in the relative use of second-line post-immunotherapy cabozantinib being underestimated.
- 6.37 The ESC considered that the assumption that the market share and uptake of cabozantinib would be the same for all six years of the financial estimates lacks face validity.

Weighted price for line-agnostic listing

- 6.38 The resubmission estimated a weighted effective price for a line-agnostic listing of \$ [REDACTED] (AEMP). This was based on the resubmission's estimates that [REDACTED]% of cabozantinib scripts will be used in the TKI-naïve setting (based on the cost-analysis versus sunitinib; \$ [REDACTED]) and [REDACTED]% in the post-TKI setting (current price; \$ [REDACTED]). The proportion of use in each setting was calculated using the number of scripts in Year 6, although this ratio was the same in every year of the financial estimates. Overall, the ESC considered that the weighted price was overestimated due to overestimation of use of cabozantinib in the higher priced post-TKI setting.

6.39 The pre-PBAC response adjusted a number of parameters (as outlined above), which resulted in a weighted effective AEMP of \$ [redacted] based on [redacted] % of cabozantinib scripts being used in the TKI-naïve setting (based on the cost-analysis versus sunitinib, which the pre-PBAC response stated resulted cabozantinib AEMP; \$ [redacted]) and [redacted] % in the post-TKI setting (current AEMP; \$ [redacted]).

Impact on utilisation

6.40 The estimated use and financial implications of the new listing using the resubmission’s estimated effective prices are presented in Table 13. This is based on the estimates proposed in the resubmission and does not reflect the changes proposed in the pre-PBAC response or the changes proposed by the PBAC.

Table 13: Estimated use and financial implications (line-agnostic listing) based on resubmission estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
NEW LISTING: TKI-naïve						
Estimated extent of use (TKI-naïve)						
Number of patients treated	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹
Number of scripts dispensed	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²
Estimated financial implications of cabozantinib (TKI-naïve)						
Cost to PBS/RPBS less copayments	[redacted] ³	[redacted] ⁴	[redacted] ⁴	[redacted] ⁴	[redacted] ⁴	[redacted] ⁴
Post-TKI setting						
Reductions in the number of scripts						
Sunitinib/pazopanib	- [redacted] ²	- [redacted] ²	- [redacted] ²	- [redacted] ²	- [redacted] ²	- [redacted] ²
Cabozantinib	- [redacted] ¹	- [redacted] ²	- [redacted] ²	- [redacted] ²	- [redacted] ²	- [redacted] ²
Estimated financial implications for reduced use of sunitinib, pazopanib and cabozantinib						
Offset due to reduced use of sunitinib and pazopanib	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³
Offset for cabozantinib (reduced use post-TKI)	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³
Total PBS/RPBS offset less copayments	\$ [redacted] ³	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴
Net financial implications – cabozantinib only						
Total PBS/RPBS – cabozantinib	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³
Net financial implications (also including offsets for sunitinib/pazopanib)						
Net cost to PBS/RPBS	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³
Net cost to MBS	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³
Net cost to PBS/RPBS/MBS	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³	[redacted] ³
Previous March 2020 resubmission						
Net cost to PBS/RPBS	[redacted] ³	[redacted] ³	- [redacted] ⁵	- [redacted] ⁵	- [redacted] ⁵	- [redacted] ⁵

Source: Section 4 cost and utilisation model.xlsx of the November 2020 resubmission; Excel spreadsheet; Table 20, cabozantinib PSD, PBAC Meeting 2020.

Abbreviations: MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

⁵ net cost saving

- 6.41 The cost to the PBS/RPBS of listing cabozantinib in the TKI-naïve setting (without offsets) was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$80 million to < \$90 million in the first 6 years of listing. The ESC considered the estimates presented in the resubmission were not reliable. The adjustments in the pre-PBAC response resulted in a cost (without offsets) of \$10 million to < \$20 million in Year 6, and a total of \$70 million to < \$80 million in the first 6 years of listing. These were based on the resubmission's estimated effective price of other therapies and the application of Clause 5.7 of the Strategic Agreement in the cost-analysis.
- 6.42 The impact is higher than what would normally be expected with a cost-minimisation analysis, noting that patients treated with cabozantinib may spend less time on post-progression treatment than those treated with sunitinib (and thus was a cost-analysis approach, rather than a cost-minimisation approach). Further, the estimates are based on the weighted price of cabozantinib (which is higher than the indication-specific price in the TKI-naïve setting), and the financial offsets only account for reductions in sunitinib and pazopanib and do not account for any potential reductions in other therapies (such as nivolumab monotherapy and axitinib).

Financial Management – Risk Sharing Arrangements

- 6.43 The resubmission proposed an RSA based on a line-agnostic listing and a weighted price across the TKI-naïve and post-TKI settings. The proposed RSA cap was based on the proposed weighted price of cabozantinib, the resubmission's revised estimates of the status quo (which were revised in the pre-PBAC response to more closely align with the script numbers agreed for cabozantinib post-TKI use under the existing RSA as shown in the first two rows of the table below), and an estimated number of scripts for a line-agnostic listing. The rebate above the proposed cap would be █████%. A summary of the proposed RSA is presented in Table 14. The table also presents the RSA cap proposed in the pre-PBAC response.

Table 14: Proposed combined RSA for a line-agnostic listing for cabozantinib

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Resubmission estimated status quo cabozantinib post-TKI scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Pre-PBAC response estimated status quo cabozantinib post-TKI scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Agreed cap in RSA for post-TKI setting (script numbers)	█ ^a	█ ^b				
Proposed cap						
Proposed cap – resubmission	█	█	█	█	█	█
Proposed cap – pre-PBAC response	█	█	█	█	█	█
Current cap	█ ^a	█ ^b	-	-	-	-
Proposed net increase to cap (resubmission)	█	█	-	-	-	-
Proposed net increase to cap (pre-PBAC response)	█	█				

Source: Table 4.23 p54 of the resubmission; Control panel of Attachment 4 - Epidemiology model.xlsx; p4 of the pre-PBAC response

Abbreviations: IO = immunotherapy; RSA = Risk Sharing Agreement; TKI = tyrosine kinase inhibitor

^a Based on Year 4 of existing deed (May 2021 to May 2022). The cap for Year 3 of the existing deed (May 2020 to May 2021) is \$█. Note that the cap for Year 2 of the existing deed (\$█) was exceeded by 2%.

^b Based on Year 5 of existing deed (May 2022 to May 2023)

The redacted values correspond to the following ranges:

² 500 to < 5,000

- 6.44 The resubmission proposed a cap of \$█ in Year 6, and a total of \$█ in the first 6 years of listing. The ESC considered that the estimates presented in the resubmission were not a reliable basis for an RSA.
- 6.45 The cap proposed in the pre-PBAC response was \$█ in Year 6, and a total of \$█ in the first 6 years of listing. However, the PBAC considered that these estimates remained overestimated as they were based on an underestimate of the market share of NIVO+IPI (and an overestimate of the market share of sunitinib and pazopanib in first-line) and an overestimate of the proportion of patients progressing to second- and third-line therapy.
- 6.46 The results of sensitivity analyses requested by the PBAC are presented in Table 15.

Table 15: Sensitivity analyses for the total cost of the new listing of cabozantinib (excluding offsets) and the RSA over the first six years – based on revised scenario presented in the pre-PBAC response

#	Tested scenario (vs value in pre-PBAC response)	Weighted DPMQ	Total costs of new listing excluding offsets	RSA cap over 6 years ^a
(% change is versus pre-PBAC response)				
	Resubmission	██████	██████	██████
Base case – pre-PBAC response				
	Existing RSA expenditure cap over 6 years (as agreed for post-TKI listing, if existing Year 5 cap of \$██████ is continued for 6 years)			~██████
1	Market share: 1L. Cabozantinib: 10% (unchanged); NIVO+IPI: 57% (vs 33%); sunitinib/pazopanib: 33% (vs 57%)	██████ (-7%)	██████ (28%)	██████ (5%)
2	TKI-naïve post-IO cabozantinib duration of treatment of 9 (vs 12) months; Post-IO & TKI cabozantinib duration of treatment of 7 (vs 8) months	██████ (2%)	██████ (-11%)	██████ (-7%)
3	65% (vs 77%) receiving 2L and 55% (vs 64%) receiving 3L	██████ (-2%)	██████ (-10%)	██████ (-14%)
4	Post-TKI cabozantinib market share of 20% (vs 40%)	██████ (-7%)	██████ (-7%)	██████ (-23%)
Multivariate sensitivity analyses				
	1+2	██████ (-6%)	██████ (11%)	██████ (-6%)
	1+3	██████ (-9%)	██████ (13%)	██████ (-10%)
	2+3	██████ (0%)	██████ (-19%)	██████ (-19%)

Source: developed using Control panel of Attachment 4 - Epidemiology model.xlsx; Section 4 cost and utilisation model.xlsx, Table 5 of the pre-PBAC response

Abbreviations: 1L = first-line treatment; 2L = second-line treatment; 3L = third-line treatment; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub Committee; IO = immunotherapy; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RSA = Risk Sharing Agreement; TKI = tyrosine kinase inhibitor

^a Based on 6 years for consistency with the financial estimates.

6.47 The ESC considered that the key issues with the financial estimates were:

- the resubmission should have used the DUSC Secretariat’s estimate of the number of first-line treated patients. This was addressed in the pre-PBAC response;
- the assumed market share of cabozantinib post-TKI of 40% was likely overestimated;
- the proportion of patients receiving second- and third-line treatment (77% and 64%, respectively) was likely overestimated. The PBAC agreed with the ESC that this was overestimated;
- first-line market shares: the estimated market share of NIVO+IPI in the first-line setting (33%) appeared to be underestimated, and the market share of sunitinib and pazopanib (57%) appeared to be overestimated. The PBAC agreed with the ESC that the first-line market shares of NIVO+IPI and sunitinib/pazopanib did not appear to be reasonable.
- the resubmission likely overestimated the duration of cabozantinib treatment in the second-line post-immunotherapy setting and the third-line (following NIVO+IPI and then a TKI) setting. While these were adjusted in the pre-PBAC

response, the PBAC considered the duration of cabozantinib therapy in these settings remained uncertain.

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

7 PBAC Outcome

- 7.1 The PBAC recommended extending the PBS listing of cabozantinib to include the treatment of patients with stage IV clear cell variant RCC who have not previously been treated with a TKI. The PBAC was satisfied that cabozantinib provides, for some patients, an improvement in PFS versus sunitinib, however an improvement in OS was not supported by the evidence presented. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of cabozantinib in the new indication would be acceptable if the cost per day for cabozantinib is no higher than the average cost per day for sunitinib. As cabozantinib is expected to be used for a longer duration due to increased PFS, the PBAC noted that cabozantinib would result in a higher total estimated drug cost per patient than sunitinib and considered that this was appropriate because it would be offset by lower post-progression costs. The PBAC considered that the weighted price (across the new and existing indications) and RSA utilisation caps should be lower than estimated in the pre-PBAC response, and that an RSA would be necessary to minimise the risks associated with the uncertain patient population.
- 7.2 The PBAC reiterated its previous consideration that the clinical need for cabozantinib was limited given the availability of other therapies for this condition. In the treatment-naïve setting, the PBAC noted that NIVO+IPI is available and that over time, immunotherapies are expected to be used in the majority of patients who are suitable for immunotherapy. In the TKI-naïve post-immunotherapy setting, the PBAC considered that the benefit of cabozantinib versus sunitinib was unknown given the limited trial evidence in this setting.
- 7.3 The resubmission nominated sunitinib as the main comparator. The PBAC considered this was appropriate.
- 7.4 The PBAC noted that no new clinical data were provided in the resubmission. 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 reiterated its previous advice that while the CABOSUN trial reported that cabozantinib was associated with a statistically significant improvement in PFS, 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. Further, the PBAC noted that the difference in OS for cabozantinib versus sunitinib was not statistically significant and appeared to be decreasing with additional follow-up.
- 7.5 In the TKI-naïve post-immunotherapy setting, the PBAC recalled that the studies presented were small, single arm, cohort studies that were not designed to investigate

the use of cabozantinib post-immunotherapy and did not provide comparative evidence versus sunitinib (or pazopanib). The PBAC reiterated its previous view that, given the paucity of evidence presented, the absolute and relative benefits of cabozantinib versus sunitinib were unknown in this setting (para 7.5, cabozantinib PSD, March 2020 PBAC meeting).

- 7.6 The PBAC considered that the claim of non-inferior (different but broadly comparable) comparative safety versus sunitinib was reasonable.
- 7.7 The resubmission presented a cost-analysis versus sunitinib that accounted for differences in treatment duration and time on post-progression therapy (assuming no difference in OS between arms). The PBAC noted that there were uncertainties regarding the proportion of patients who require post-progression treatment and the cost of post progression treatment, but overall accepted that the analysis adequately demonstrated that cabozantinib is cost-effective if the cost per day for cabozantinib that is no higher than the average cost per day for sunitinib.
- 7.8 The PBAC considered that the resubmission's assumption that the following doses (based on the average daily doses in CABOSUN) would achieve similar OS outcomes was reasonable:
- cabozantinib 49.4 mg daily; and
 - sunitinib 43.7 mg daily for 4 weeks of a 6-week treatment cycle.
- 7.9 The PBAC noted that these daily doses were then applied to the time on treatment from CABOSUN extrapolated over a 7.5 year time horizon, with cabozantinib-treated patients staying on treatment for 12.6 months⁴, and sunitinib-treated patients staying on treatment for 7.2 months⁴. This will likely result in a higher total estimated drug cost per patient for cabozantinib, which the PBAC considered to be appropriate, because it would be offset by lower post-progression costs. The resubmission assumed cabozantinib would require a shorter duration of post-progression treatment than sunitinib (16.8⁴ versus 24.5⁴ months, respectively). The PBAC considered this was reasonable given the likely small (though uncertain) increase in PFS and the absence of a demonstrated OS benefit.
- 7.10 The PBAC considered that the revised financial estimates in the pre-PBAC response had addressed the ESC's concerns regarding the overestimated number of patients commencing first-line treatment, and the overestimated market share of cabozantinib in the third-line setting (following NIVO+IPI and then a TKI). However, the PBAC considered that the pre-PBAC response's estimates continued to overestimate the relative use of cabozantinib in the post-TKI setting (which has a higher price), and thus overestimated the weighting applied to the price of cabozantinib in the post-TKI

⁴ Note that the mean duration of treatment was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

setting (■%) relative to the TKI-naive setting (■%) in forming the combined weighted price. This overestimated the weighted price. The PBAC considered that the key reasons for this were:

- the proportion of patients receiving second- and third-line treatment (77% and 64%, respectively) was likely overestimated; and
- first-line market shares: the estimated market share of NIVO+IPI in the first-line setting (33%) appeared to be underestimated, and the market share of sunitinib and pazopanib (57%) appeared to be overestimated.

7.11 In addition, the PBAC considered that the resubmission likely overestimated the duration of cabozantinib treatment in the second-line post-immunotherapy setting and the third-line (following NIVO+IPI and then a TKI) settings. While these were adjusted in the pre-PBAC response, the PBAC considered that the duration of cabozantinib therapy in these settings remained uncertain.

7.12 The PBAC considered that precise values for many of these parameters were highly uncertain. The PBAC noted the sensitivity analyses presented in Table 15, and overall, considered that the range of more appropriate parameters would result in a reduction to the weighted price in the order of 6% to 9% compared with the pre-PBAC response. In particular, the PBAC considered that a scenario on which to base the weighted price and financial estimates should include the following assumptions:

- 65% and 55% of patients receive second-line and third-line treatment, respectively;
- a market share of NIVO+IPI in the first-line setting of 57%; and
- a market share of sunitinib and pazopanib in the first-line setting of 33%.

7.13 The PBAC advised that a RSA with a ■% rebate for utilisation above the agreed estimates would be necessary to minimise the risks associated with the uncertain patient population. The PBAC considered that only a small increase in the currently agreed caps would be justified given the increasing role of immunotherapy in the treatment of RCC. The PBAC advised that a new RSA cap encompassing all lines of therapy should be based on the pre-PBAC response financial estimates, which should be further adjusted taking into account the recommended changes as per paragraph 7.12. The PBAC re-iterated that a combined RSA would be necessary across the proposed and existing cabozantinib indications to ensure that the offsets in the existing later-line setting are realised.

7.14 The PBAC noted that this submission is not eligible for an Independent Review as a positive recommendation was made.

7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that:

- a) Treatment with cabozantinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative therapies.

b) Treatment with cabozantinib is not expected to address a high and urgent unmet clinical need.

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOZANTINIB					
cabozantinib 20 mg tablet, 30	11371L	1	30	2	Cabometyx
cabozantinib 40 mg tablet, 30	11369J	1	30	2	Cabometyx
cabozantinib 60 mg tablet, 30	11360X	1	30	2	Cabometyx
Restriction Summary 8589 / Treatment of Concept: 8572					
Category / Program: General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [8572 currently; to be updated]					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
PBS Indication: Stage IV clear cell variant renal cell carcinoma (RCC)					
Treatment phase: Initial treatment					
Clinical criteria:					
Patient must have progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) following prior treatment with a tyrosine kinase inhibitor					
AND					
Clinical criteria:					
Patient must have a WHO performance status of 2 or less					
AND					
Clinical criteria:					
Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 0 (favourable risk), (ii) 1 to 2 (intermediate risk), (iii) 3 to 6 (poor risk), documented in the patient's medical records at the time of prescribing					
AND					
Clinical criteria:					
The treatment must not be prescribed for a patient with favourable risk disease (IMDC score of 0) prior to use of any of: (i) pazopanib, (ii) sunitinib					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition.					
Treatment criteria:					
Patient must be undergoing treatment with this drug for the first time					
Administrative Advice:					
Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions					

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	<p>Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions Stable disease (SD) is small changes that do not meet above criteria.</p>
	<p>Administrative advice: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-renal-cell-carcinoma.</p> <p>One point is assigned for each of: (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80% (iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal</p> <p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6.</p> <p>The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOZANTINIB					
cabozantinib 20 mg tablet, 30	11374P	1	30	5	Cabometyx
cabozantinib 40 mg tablet, 30	11368H	1	30	5	Cabometyx
cabozantinib 60 mg tablet, 30	11367G	1	30	5	Cabometyx

Restriction Summary 7638 / ToC: 7631: Authority Required: Streamlined – NO CHANGE

	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug
	<p>Administrative Advice: Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.</p>

Administrative Advice: Special Pricing Arrangements apply.

8.2 Flow-on changes to existing listings for sunitinib & pazopanib in renal cell carcinoma indication are as follows:

Amendments to the existing sunitinib listings:

Amend the following Prescribing Instructions as follows:

Medicinal Product: Sunitinib	
Indication: Stage IV clear cell variant renal cell carcinoma (RCC) [7597]	Treatment Phase: Initial treatment
Affected PBS item codes: 9417P, 9418Q, 10504W, 9419R	Affected Restriction Summary Number: 9210

Prescribing Instructions: Patients who have developed progressive disease on pazopanib are not eligible to receive PBS subsidised sunitinib.
Prescribing Instructions: PBS-subsidy does not apply to a patient who has progressive disease whilst on, or, who has recurrent disease following treatment with any of: (i) cabozantinib, (ii) pazopanib, (iii) sunitinib

Medicinal Product: Sunitinib	
Indication: Stage IV clear cell variant renal cell carcinoma (RCC) [7597]	Treatment Phase: Continuing treatment beyond 3 months
Affected PBS item codes: 9420T, 9421W, 10459L, 9422X	Affected Restriction Summary Number: 7485

Prescribing Instructions: Patients who have developed progressive disease on pazopanib are not eligible to receive PBS subsidised sunitinib.

Amendments to the existing pazopanib listings:

Amend the following Prescribing Instructions as follows:

Medicinal Product: Pazopanib	
Indication: Stage IV clear cell variant renal cell carcinoma (RCC) [7597]	Treatment Phase: Initial treatment
Affected PBS item codes: 2029T, 2030W	Affected Restriction Summary Number: 9281

Prescribing Instructions: Patients who have progressive disease on sunitinib are not eligible to receive PBS subsidised pazopanib.
Prescribing Instructions: PBS-subsidy does not apply to a patient who has progressive disease whilst on, or, who has recurrent disease following treatment with any of: (i) cabozantinib, (ii) pazopanib, (iii) sunitinib

Medicinal Product: Pazopanib	
Indication: Stage IV clear cell variant renal cell carcinoma (RCC) [7597]	Treatment Phase: Continuing treatment beyond 3 months
Affected PBS item codes: 11252F, 11261Q	Affected Restriction Summary Number: 7482

Prescribing Instructions: Patients who have progressive disease on sunitinib are not eligible to receive PBS subsidised pazopanib.

Amendments to the existing ipilimumab listings for induction treatment in renal cell carcinoma to include directions on the calculation of an IMDC risk score for consistency with cabozantinib:

Medicinal Product: Ipilimumab	
Indication: Stage IV clear cell variant renal cell carcinoma (RCC) [7597]	Treatment Phase: Induction treatment
Affected PBS item codes: 11627Y, 11636K (360 mg)	Affected Restriction Summary Number: 8609

Medicinal Product: Ipilimumab	
Indication: Stage IV clear cell variant renal cell carcinoma (RCC) [7597]	Treatment Phase: Induction treatment
Affected PBS item codes: 11628B, 11644W (120 mg)	Affected Restriction Summary Number: 8574

Administrative advice:

A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: <https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma>.

One point is assigned for each of:

- (i) a time of diagnosis to systemic therapy of less than 1 year
- (ii) a Karnofsky Performance Status of less than 80%
- (iii) a haemoglobin less than the lower limit of normal
- (iv) a corrected calcium level greater than the upper limit of normal
- (v) a neutrophil count greater than the upper limit of normal
- (vi) a platelet count greater than the upper limit of normal

Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.

Favourable IMDC risk is a score of 0.
Intermediate IMDC risk is a score of 1 to 2.
Poor IMDC risk is a score of 3 to 6.

The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.