

## 5.02 CABOZANTINIB, Tablet 20 mg, 40 mg and 60 mg, Cabometyx<sup>®</sup>, Ipsen Pty Ltd

### 1 Purpose of application

- 1.1 The submission requested a Section 85, Authority Required (Streamlined), listing of cabozantinib for treatment of patients with Stage IV (unresectable) clear cell variant renal cell carcinoma (RCC), who have progressive disease following first-line treatment with a tyrosine kinase inhibitor (TKI). This submission had not previously been considered by the PBAC.
- 1.2 The submission presented a cost-effectiveness analysis of cabozantinib compared with everolimus, and both a cost-effectiveness analysis and a cost-minimisation analysis of cabozantinib compared with nivolumab.

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

Component	Description
Population	Patients with Stage IV (unresectable) clear cell variant RCC, whose disease is progressive following first-line treatment with a TKI.
Intervention	Cabozantinib 60 mg orally once daily.
Comparator	Main comparator: Everolimus 10 mg orally once daily Near market comparator: Nivolumab 3 mg/kg administered intravenously every 2 weeks Other/Secondary comparator: Axitinib 5 mg orally twice daily.
Outcomes	Overall survival, progression free survival and objective response rate. Overall survival is the key patient-relevant outcome.
Clinical claim	In adult patients with metastatic clear cell variant RCC who experience disease progression on or after prior VEGFR-targeted treatment: <ul style="list-style-type: none"> <li>• Compared with everolimus, cabozantinib is superior in terms of effectiveness (PFS, OS and ORR), and is non-inferior in term of safety.</li> <li>• Compared with nivolumab, cabozantinib is non-inferior in terms of OS and ORR, superior in terms of PFS, and inferior in terms of safety.</li> </ul>

ORR = objective response rate; OS = overall survival; PFS = progression free survival; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

Source: Table 1-1 p20 and Section 2.8.2 p152 of the submission

## 2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
CABOZANTINIB			Cabometyx	Ipsen Australia Pty Ltd
Cabozantinib, 60 mg tablet, 30	30	2		
Cabozantinib, 40 mg tablet, 30	30	2		
Cabozantinib, 20 mg tablet, 30	30	2		

<b>Category / program</b>	General Schedule
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	<del>Monthly</del>
<b>Severity:</b>	Stage IV
<b>Condition:</b>	Clear cell variant renal cell carcinoma (RCC)
<b>PBS Indication:</b>	Stage IV clear cell variant renal cell carcinoma (RCC)
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	NA
<b>Clinical criteria:</b>	Patient must have progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) following first line treatment with a Tyrosine Kinase Inhibitor (TKI); AND Patient must have disease which is WHO performance status of 2 or less; AND Treatment must be the sole PBS-subsidised therapy for this condition
<b>Population criteria:</b>	NA
<b>Prescriber Instructions</b>	<del>Patients who have developed intolerance to a TKI of a severity necessitating permanent treatment; AND withdrawal are eligible to receive PBS subsidised cabozantinib;</del>  <del>Patients who have progressive disease with cabozantinib are no longer eligible for PBS subsidised cabozantinib.</del>
<b>Administrative Advice</b>	
<b>Definitions</b>	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.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
CABOZANTINIB			Cabometyx Ipsen Australia Pty Ltd
Cabozantinib, 60 mg tablet, 30	30	5	
Cabozantinib, 40 mg tablet, 30	30	5	
Cabozantinib, 20 mg tablet, 30	30	5	

<b>Category / program</b>	General Schedule
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Monthly
<b>Severity:</b>	Stage IV
<b>Condition:</b>	Clear cell variant renal cell carcinoma (RCC)
<b>PBS Indication:</b>	Stage IV clear cell variant renal cell carcinoma (RCC)
<b>Treatment phase:</b>	Continuing treatment <del>beyond 3 months</del>
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	NA
<b>Clinical criteria:</b>	Patient must have previously <i>received PBS-subsidised treatment with this drug for this condition</i> AND Patient must have stable or responding disease according to the Response Evaluation Criteria in Solid Tumours (RECIST), AND Treatment must be the sole PBS-subsidised therapy for this condition. AND <i>Patients must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.</i>
<b>Population criteria:</b>	NA
<b>Prescriber Instructions</b>	<del>A patient who has progressive disease when treated with this cabozantinib is no longer eligible for PBS-subsidised treatment with cabozantinib.</del>
<b>Administrative Advice</b>	NA
<b>Definitions</b>	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.

2.2 The recommended dose of cabozantinib in the draft product information (PI) is 60 mg once daily.

2.3 Cabozantinib was proposed as a second-line treatment option in patients with clear cell variant metastatic RCC, who have progressive disease following first-line treatment with a TKI. The requested restriction does not restrict use of cabozantinib to patients who have only received one prior line of therapy. In particular, it does not preclude the use of cabozantinib subsequent to treatment with second-line nivolumab (after a first-line TKI).

- 2.4 If cabozantinib is listed, it is likely that nivolumab and cabozantinib will be used sequentially (in either order) in these patients, i.e. as second- and third-line treatment, consistent with the recommendations in European Society of Medical Oncology (ESMO) guidelines for RCC\*.
- 2.5 Under the requested listing, eligibility for initiation of cabozantinib would be limited to patients with Stage IV disease and with a World Health Organisation (WHO) performance status of 2 or less. In the key cabozantinib trial, 85% of patients were confirmed to have Stage IV disease. Choueiri 2016<sup>†</sup> reported that all patients had an Eastern Cooperative Oncology Group (ECOG)/WHO performance status of 0 or 1.
- 2.6 The clinical criteria proposed in the restriction included ongoing stable or responding disease according to RECIST. The ESC noted that patients are likely to be assessed for radiographic progression less regularly in clinical practice compared to in trials.
- 2.7 The submission stated that the sponsor intends to enter into a special pricing arrangement for cabozantinib, but noted that the effective price could not be established until the effective prices for currently listed treatments are known.

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

### **3 Background**

#### **Registration status**

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA clinical evaluator's report (Round 1) was available. The TGA Delegate's Overview for cabozantinib was provided with the Pre-Sub-Committee Response (PSCR), while the delegate's decision is expected in January 2018.
- 3.2 The proposed TGA indication for cabozantinib was for treatment of advanced RCC in adults following prior therapy. The TGA evaluator recommended that the indication should be amended to: the treatment of advanced RCC in adults following prior treatment with vascular endothelial growth factor receptor (VEGFR)-targeted therapy (Section 11.1, p112 TGA Clinical Evaluation Report). The proposed indication presented in the Delegate's Overview was consistent with this recommendation.

### **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 80-95% of all cases. Kidney cancer is more frequently reported in males than in females. In 2013, there were 2,256 cases of kidney cancer in males and 1,256 cases in females. Most RCC patients are diagnosed with advanced disease, and this is often resistant to systemic therapy.

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\* Escudier B, Porta C, *et al.* Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016; 27 (suppl 5):v58-v68.

<sup>†</sup> Choueiri TK, Escudier B, *et al.* Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2016; 17 (7):917-27.

- 4.2 First line treatment options for advanced RCC include the currently PBS listed tyrosine kinase inhibitors (TKIs), sunitinib and pazopanib. At the time the submission was lodged, PBS listed items for second line therapy included everolimus, axitinib and sorafenib.
- 4.3 Most recently, in March 2017, the PBAC recommended the listing of nivolumab as a treatment option for patients with advanced RCC in a second line setting, as a potential alternative to the currently available drugs. The PBAC considered that for some patients nivolumab provided a significant improvement in efficacy and a reduction in toxicity over everolimus, which was the nominated comparator (paragraph 7.1, nivolumab Public Summary Document, March 2017).
- 4.4 The ESMO, National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines for RCC all recommend the use of nivolumab or cabozantinib in preference to everolimus or axitinib in patients who have progressed following first-line treatment with a VEGF-targeted therapy<sup>‡</sup>.
- 4.5 The submission indicated that cabozantinib would be an alternative to nivolumab in the second-line setting, displacing everolimus, axitinib and sorafenib to third- and later-lines of therapy. The submission also indicated that cabozantinib may also be used as third-line therapy in patients with progressive disease following second-line nivolumab (and vice versa).

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

## 5 Comparator

- 5.1 The submission nominated everolimus as the main comparator, axitinib as a secondary comparator, and nivolumab as a near market comparator.
- 5.2 Given its recent PBS-listing, nivolumab was considered the most relevant comparator in the second-line setting, following first-line treatment with a TKI.
- 5.3 Everolimus is an appropriate alternative comparator for cabozantinib in the second-line setting, especially for patients who prefer an oral, rather than an intravenous, treatment. Everolimus and axitinib would be appropriate comparators for cabozantinib in the third-line setting, following prior treatment with a first-line TKI and second-line nivolumab. Only 5% of patients in the METEOR trial had previously received both a TKI and nivolumab.
- 5.4 The comparison of cabozantinib with axitinib, based on an indirect comparison via an evidence network, was presented in Attachment 11 to the submission. The submission stated that this comparison was considered supportive information only.

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<sup>‡</sup> Escudier B, Porta C, *et al.* Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016; 27 (suppl 5):v58-v68

Motzer RJ, Jonasch E, *et al.* NCCN Clinical practice guidelines on oncology: Kidney cancer. Version 2.2017 2017 [updated 31 October, 2016; cited 11 September 2017]. Available from: [www.nccn.org](http://www.nccn.org).

Ljungberg B, Albiges L, *et al.* EUA Guidelines on renal cell carcinoma 2017 [cited 11 September 2017]. Available from: <https://uroweb.org/guideline/prostate-cancer/>.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed some of the relative benefits of immunotherapies and other therapies, including circumstances under which one or the other might be used and also the importance of having an option other than an immunotherapy for these patients, and addressed other matters in response to the Committee's questions. The clinician highlighted that the toxicity profile of cabozantinib was manageable through dose reductions and similar to that of other TKIs. The PBAC considered that the hearing was informative as it assisted in determining the proportion of patients likely to receive cabozantinib and nivolumab in the 2<sup>nd</sup> or 3<sup>rd</sup> line setting.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from an individual (1), health care professional (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments discussed the importance of the availability of treatment options for this patient population, and the benefits and tolerability of cabozantinib.

### ***Clinical trials***

- 6.3 The submission was based on one head-to-head, open-label randomised controlled trial (RCT) comparing cabozantinib with everolimus in patients with advanced or metastatic clear cell variant RCC who had progressed after prior VEGFR-targeting TKI therapy (METEOR; N=658).
- 6.4 The submission also presented an indirect comparison of cabozantinib versus nivolumab, with everolimus as the common comparator, using the METEOR trial, and an open-label RCT comparing nivolumab with everolimus in patients with advanced or metastatic clear cell variant RCC who had received one or two previous regimens of antiangiogenic therapy (CheckMate 025; N=821). The CheckMate study was presented in the nivolumab submission considered by PBAC at the March 2017 meeting.
- 6.5 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
METEOR Cabozantinib versus everolimus	<p>Clinical study report: A phase 3, randomised, controlled study of cabozantinib (XL184) vs. everolimus in patients with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy.</p> <p>Clinical study report addendum.</p> <p>Choueiri TK, Escudier B, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma.</p> <p>Choueiri TK, Escudier B, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial.</p> <p><u>Abstracts</u></p> <p>Powles T, Motzer RJ, et al. Outcomes based on prior VEGFR TKI and PD-1 checkpoint inhibitor therapy in METEOR, a randomised Phase 3 trial of cabozantinib vs everolimus in advanced renal cell carcinoma.</p> <p>Escudier B, Powles T, et al. Efficacy of cabozantinib vs everolimus in patients with advanced renal cell carcinoma and bone metastases from the Phase 3 METEOR trial.</p>	<p>December 2015.</p> <p>February 2016.</p> <p>New England Journal of Medicine 2015; 373:1814-1823.</p> <p>Lancet Oncology 2016; 17:917-927.</p> <p>American Society of Clinical Oncology (ASCO) Meeting, Chicago, IL, USA, 3-7 June 2016.</p> <p>American Society of Clinical Oncology (ASCO) Meeting, Chicago, IL, USA, 3-7 June 2016.</p>
CheckMate 025 Nivolumab versus everolimus	<p>Motzer RJ, Escudier B, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma.</p> <p>Escudier B, Sharma P, et al. CheckMate 025 randomized phase 3 study: Outcomes by key baseline factors and prior therapy for nivolumab versus everolimus in advanced renal cell carcinoma.*</p> <p>Cella D, Grünwald V, et al. Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: a randomised, open-label, phase 3 trial.</p> <p><u>Abstract</u></p> <p>Motzer RJ, Sharma P, et al. Correlation of response with overall survival (OS) for nivolumab vs everolimus in advanced renal cell carcinoma (aRCC): Results from the phase III CheckMate 025 study.</p>	<p>New England Journal of Medicine 2015; 373:1803-1813.</p> <p>European Urology 2017; 72 (3): 368-376.</p> <p>Lancet Oncology 2016; 17:994-1003.</p> <p>Journal of Clinical Oncology 2016; 34 (suppl abstr 4552):1-2.</p>

aRCC = advanced renal cell carcinoma; PD-1 = programmed death 1; OS = overall survival; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor

\*The Clinical Protocol and the Statistical Analysis Plan for CheckMate 025 were provided as supplementary materials to Escudier 2017.

Source: Table 2-3, p62 of the submission

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

**Table 3: Key features of the included evidence**

Trial	N	Design/ minimum duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Cabozantinib versus everolimus</b>						
METEOR	ITT: 658 PITT: 375	R, OL <sup>a</sup> , MC May 2015 database lock: ITT: 5.9 mths PITT <sup>b</sup> :10.7 mths Dec 2015 database lock: ITT: 13.0 mths	Moderate	Advanced/metastatic RCC following at least one prior VEGFR-targeted treatment	PFS (primary) <sup>b</sup> OS, ORR, EQ5D	PFS, OS, EQ5D used
<b>Nivolumab versus everolimus</b>						
CheckMate 025	ITT: 821	R, OL, MC 14 mths	Moderate	Advanced/metastatic RCC following at least one prior antiangiogenic treatment	OS (primary) PFS, ORR	PFS, OS used

ITT = intention to treat; MC = multi-centre; mths = months; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PITT= primary intention to treat; R = randomised; RCC = renal cell carcinoma; VEGFR = vascular endothelial growth factor receptor.

<sup>a</sup> Tumour response and progression were assessed by a blinded centralised independent review committee

<sup>b</sup> The primary outcome was PFS in the primary intention to treat (PITT) population, which was defined as the first 375 randomised patients.

Source: compiled during the evaluation.

6.7 Both trials included patients with advanced/metastatic RCC with a clear-cell component and with progressive disease following prior treatment. Patients in METEOR must have received at least one prior VEGFR-targeting TKI. Patients in CheckMate 025 were required to have received at least one, but no more than two, prior antiangiogenic treatments and must have received no more than three total prior systemic treatments in the advanced disease/metastatic setting. A considerable proportion of patients in both trials had previously received more than one prior TKI/antiangiogenic treatment.

6.8 85% of patients in METEOR were confirmed to have Stage IV disease. Choueiri 2016<sup>§</sup> reported that all patients in METEOR had a WHO performance status of 0 or 1. Baseline disease stage and WHO performance status were not reported for CheckMate 025.

6.9 In both METEOR and CheckMate 025, patients were allowed to continue treatment beyond progression if the investigator believed that the patient was still receiving clinical benefit from the study drug. The ESC noted that this was not consistent with the restriction, which requires patients to have stable or responding disease, according to RECIST.

6.10 Given the open-label design of both trials, there was a high risk of performance bias, especially in regard to patient management decisions. There was also a risk of bias in the assessment of safety outcomes in terms of grading of severity and attribution of causality of adverse events (AEs).

<sup>§</sup> Choueiri TK, Escudier B, *et al.* Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2016; 17 (7):917-27.

- 6.11 In METEOR, tumour response and progression were assessed by a blinded centralised independent review committee, thereby reducing the risk of detection bias in the assessment of tumour response and progression free survival (PFS). In contrast, radiologic outcomes in CheckMate 025 were assessed by the investigator and were, therefore, potentially subject to bias.
- 6.12 As tumour responses to immunotherapies can occur after conventional RECIST-defined progressive disease (i.e. the tumour flare effect), RECIST-defined PFS is not a reliable measure of the clinical effectiveness of nivolumab<sup>\*\*</sup>.
- 6.13 Neither trial permitted patients in the everolimus arm to switch to the intervention after progression. At the December 2015 database lock for the second interim analysis of overall survival (OS) in the METEOR trial, only 7/328 patients (2.1%) in the everolimus arm of METEOR had subsequently received cabozantinib. Similarly, at the June 2015 database lock in CheckMate 025, only 7/441 patients (1.8%) in the everolimus arm had subsequently received a programmed death 1 (PD-1) inhibitor. Therefore, there was minimal risk of confounding of OS due to treatment switching in either of the trials.

## ***Comparative effectiveness***

### Cabozantinib versus everolimus

- 6.14 Overall survival was a secondary outcome in METEOR. An initial prespecified interim analysis was conducted at the May 2015 data cut-off for the primary analysis of PFS. As this interim analysis of OS failed to reach the pre-specified criterion for statistical significance, a second, unplanned, interim analysis was performed, with a December 2015 cut-off date.
- 6.15 Table 4 presents the OS results from METEOR. The Kaplan-Meier plot of OS for the December 2015 data cut-off is presented in Figure 1.

**Table 4: OS results from METEOR (ITT population)**

	May 2015 data cut-off		December 2015 data cut-off	
	Cabozantinib N=330	Everolimus N=328	Cabozantinib N=330	Everolimus N=328
Minimum duration of follow-up, months	5.9 months		13 months	
Number of events, n (%)	89 (27%)	113 (34%)	140 (42%)	180 (55%)
Median OS, months (95% CI)	NE	NE	21.4 (18.7, NE)	16.5 (14.7, 18.8)
HR (95% CI, stratified) <sup>a</sup>	0.68 (0.51, 0.90)		0.67 (0.53, 0.83)	
p-value (stratified log-rank test) <sup>a</sup>	0.006 <sup>b</sup>		0.0003 <sup>c</sup>	
HR (95% CI, unstratified)	0.69 (0.53, 0.92)		0.67 (0.54, 0.84)	
p-value (unstratified log-rank test)	0.010		0.0004	

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable; OS = overall survival

<sup>a</sup> Stratification factors include number of prior VEGFR-targeting TKI treatments (1 vs  $\geq 2$ ) and Memorial Sloan-Kettering Cancer Center prognostic criteria (0 vs 1 vs 2).

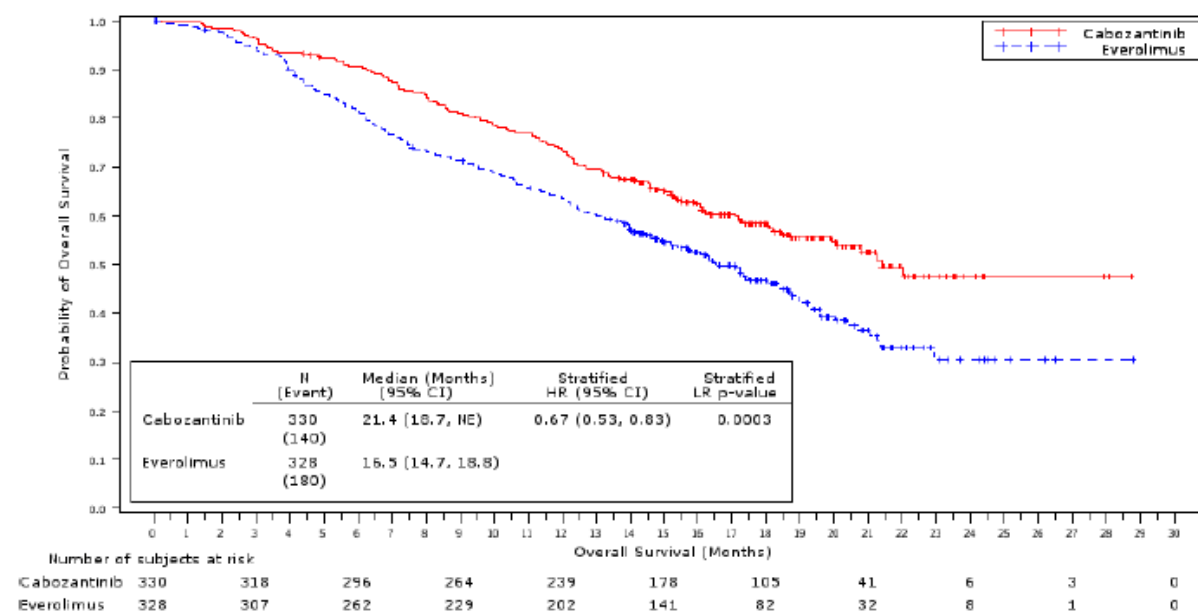
<sup>b</sup> The p-value required to achieve statistical significance at the time of the interim analysis was  $p \leq 0.0019$ .

<sup>c</sup> The critical value for rejecting the null hypothesis at the second, unplanned, interim analysis was  $p < 0.0163$ .

Source: Table 28, p123 of the METEOR CSR; Table 2 p10 METEOR CSR Addendum.

<sup>\*\*</sup> Wolchok JD, Hoos A, *et al.* Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. *Clinical Cancer Research*. 2009; 15 (23):7412-20

Figure 1: Kaplan-Meier plot of OS, METEOR, ITT population (December 2015 data cut-off)



CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable; LR = log-rank; OS = overall survival.  
 Source: Figure 2-6, p106 of the submission.

- 6.16 The critical value for rejecting the null hypothesis at the second, unplanned, interim analysis was  $p < 0.0163$ . Therefore, this analysis demonstrated a statistically significant difference in the duration of OS for cabozantinib compared with everolimus, with an estimated 4.9 months difference in median OS between the treatment arms, as of the December 2015 data cut-off.
- 6.17 The OS data at the December 2015 data cut-off were still relatively immature, with 78% (320/408) of the total deaths required for the planned final analysis of OS having occurred. Given this, it is possible that the extent of OS benefit observed in the unplanned interim analysis may not be observed in the clinical setting. The ESC requested that the sponsor provide any update to the safety data with their Pre-PBAC Response.
- 6.18 In METEOR, the primary outcome was PFS in the primary intention-to-treat (PITT) population, which included the first 375 randomised patients, performed at the May 2015 data cut-off. A sensitivity analysis of PFS based on the intention to treat (ITT) population (all randomised patients) was also performed at this time.
- 6.19 The results of the primary analysis of PFS, based on the PITT population, and the ITT analysis, which was provided as sensitivity analysis, are summarised below.

**Table 5: PFS results from METEOR (May 2015 data cut-off)<sup>a</sup>**

	Cabozantinib	Everolimus
<b>Primary Endpoint (PITT population)</b>	<b>N=187</b>	<b>N=188</b>
Minimum duration of follow-up	10.7 months	
Number of events, n (%)	121 (65%)	126 (67%)
Median PFS (95% CI)	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)
Hazard ratio (95% CI; stratified <sup>b</sup> /unstratified)	0.59 (0.46, 0.76) / 0.59 (0.46, 0.76)	
Log-rank p-value (stratified <sup>b</sup> /unstratified)	< 0.001 / < 0.001	
<b>Sensitivity Analysis (ITT Population)</b>	<b>N=330</b>	<b>N=328</b>
Minimum duration of follow-up	5.9 months	
Number of events, n (%)	180 (55%)	214 (65%)
Median PFS (months)	7.4 (6.6, 9.1)	3.9 (3.7, 5.1)
Hazard ratio (95% CI; stratified <sup>b</sup> /unstratified)	0.52 (0.43, 0.64) / 0.52 (0.42, 0.63)	
Log-rank p-value (stratified <sup>b</sup> /unstratified)	<0.001 / <0.001	

CI = confidence interval; ITT = intention-to-treat; PFS = progression free survival; PITT = primary intention-to-treat;

<sup>a</sup> As assessed by the blinded Independent Review Committee

<sup>b</sup> Stratification factors include number of prior VEGFR-targeting TKI treatments (1 vs ≥2) and Memorial Sloan-Kettering Cancer Center prognostic criteria (0 vs 1 vs 2).

Source: Table 2-14 p101 of the submission; Table 21 p112 and Table 23 p115 METEOR CSR

6.20 Results for the PITT and ITT populations were similar. Cabozantinib was statistically superior to everolimus in terms of PFS, with an estimated 3.5 months difference in median PFS between the treatment arms, based on the ITT analysis.

#### Indirect comparison of cabozantinib versus nivolumab

6.21 The submission stated that METEOR and CheckMate 025 were of generally comparable design, with broadly consistent eligibility criteria, identical comparator treatment regimens and similar outcomes and methods of statistical analysis. The main demographic and disease characteristics of patients, and the event rates in the control group in the two trials were also considered to be generally similar.

6.22 There was a slightly greater proportion of patients with a favourable Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk in METEOR compared to CheckMate 025. There were also some differences in prior and subsequent treatments received between the two trial populations. Given the lack of details available, it was not possible to assess the similarity of the two common comparator arms in terms of the extent of post-progression exposure to everolimus. The likely impact of these differences on the results of the indirect comparison was unclear.

6.23 In any indirect comparison, there is potential for confounding due to imbalances in unobserved prognostic factors or treatment effect modifiers across the studies, or undocumented differences in study conduct.

6.24 The results of the indirect comparison of OS at the latest data cut are presented in Table 6. Given the immaturity of the OS data at the May 2015 data cut-off for METEOR, the indirect comparison based on these results have not been included in the table. The estimated indirect HR for OS based on these data was 0.93 (95% confidence interval (CI): 0.64, 1.36).

**Table 6: Results of the indirect comparison of cabozantinib and nivolumab: overall survival**

	METEOR (ITT)		CheckMate 025 (ITT)	
	Cabozantinib N=330	Everolimus N=328	Nivolumab N=410	Everolimus N=411
	December 2015 data cut-off		June 2015 data cut-off	
Minimum duration of follow-up, months	13 months		14 months	
Number of events, n (%)	140 (42.4%)	180 (54.9%)	183 (44.6%)	215 (52.3%)
Median OS, months (95% CI)	21.4 (18.7, NE)	16.5 (14.7, 18.8)	25.0 (21.8, NE)	19.6 (17.6, 23.1)
HR (95% CI, stratified)	0.67 (0.53, 0.83) <sup>a</sup>		0.73 (0.57, 0.93) <sup>b</sup>	
p-value (stratified log-rank test)	0.0003 <sup>a</sup>		0.002 <sup>b</sup>	
Cabozantinib vs nivolumab, HR (95% CI)	0.92 (0.66, 1.28)			

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable; OS = overall survival

<sup>a</sup> Stratification factors include prior VEGFR-targeting TKI therapy (1 vs  $\geq 2$ ) and MSKCC prognostic criteria (0 vs 1 vs 2).

<sup>b</sup> Stratified by MSKCC prognostic criteria; number of prior antiangiogenic therapies in the advanced/metastatic setting and region.

Source: Table 2-51 p143 of the submission; Table 28, p123 of the METEOR CSR; Table 2 p10 and Table 3 p11 METEOR CSR Addendum; Figure 1, Motzer 2015<sup>††</sup>.

- 6.25 The submission stated that the hazard ratio for OS suggested a non-inferior health outcome for cabozantinib and nivolumab, although the precision of this estimate was relatively poor. The submission did not nominate a non-inferiority margin for this comparison. The indirect comparison lacked the statistical power to rule out an important difference in survival between patients receiving cabozantinib or nivolumab, with the 95% CI for the indirect estimate of the HR ranging from 0.66 to 1.28 (based on the December 2015 cut-off for METEOR). The ESC noted that the PSCR (p1) presented a follow-up analysis of overall survival from METEOR, based on data to October 2016, and that the results of the indirect comparison using this later cut-off were consistent with the analysis presented in the submission. However, the ESC remained concerned with the reliability of the indirect comparison, given that only HR point estimates and 95% CIs were provided, without further statistical support.
- 6.26 Given the issues regarding the reliability of RECIST-defined PFS as a measure of the clinical effectiveness of nivolumab, the indirect comparison of PFS for cabozantinib versus nivolumab is of limited clinical relevance. The ESC additionally considered that the wide CIs and differences between the common comparator arms limited the reliability of these results.

## ***Comparative harms***

### **Cabozantinib versus everolimus**

- 6.27 The main safety outcomes in METEOR are summarised in Table 7.

<sup>††</sup> Motzer RJ, Escudier B, *et al.* Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2015; 373 (19):1803-13

**Table 7: Summary of key adverse events in METEOR (safety population)**

	Cabozantinib N=331 n (%)	Everolimus N=322 n (%)
Median duration of exposure	7.6 months <sup>a</sup>	4.4 months <sup>a</sup>
Any treatment related AE	322 (97%)	293 (91%)
Treatment related Grade 3 or 4 AE	195 (59%)	131 (41%)
Treatment related serious AE	50 (15%)	41 (13%)
Treatment discontinuation due to AE not related to RCC	34 (10%)	31 (9.6%)
Grade 5 AE at any time <sup>b</sup>	23 (6.9%)	28 (8.7%)
Treatment related Grade 5 AE	1 (0.3%)	2 (0.6%)

AE = adverse event; RCC = renal cell carcinoma

<sup>a</sup> Source: Choueiri 2015<sup>1</sup>

<sup>b</sup> Grade 5 AEs were not necessarily reported for subject deaths due to progressive disease.

Source: Table 2-26 p125 and Table 2-33 p131 of the submission; Table 51, p172 METEOR CSR.

- 6.28 The most common treatment-related Grade 3 or 4 AEs with cabozantinib were hypertension (14%), diarrhoea (11%), palmar-plantar erythrodysesthesia syndrome (8.2%), fatigue (7.9%), and hypomagnesaemia (3.3%), and with everolimus were anaemia (9.3%), fatigue (4.3%), hyperglycaemia (3.4%), and mucosal inflammation (3.4%). A greater proportion of patients receiving cabozantinib experienced a treatment-related Grade 3-4 AE (59%) than patients receiving everolimus (41%). The ESC noted there was a difference in median exposure between the treatment arms, with greater exposure in the cabozantinib arm and that the rate of serious AEs was similar.
- 6.29 Discontinuation due to AEs was reported for 34/331 patients (10.3%) who received cabozantinib and 31/322 patients (9.6%) of patients who received everolimus. A total of 59.8% of patients in the cabozantinib arm and 24.2% in the everolimus arm had a dose reduction due to an AE. A second dose reduction due to an AE occurred in 19.3% and 1.6% of patients in the cabozantinib and everolimus arms, respectively. The TGA evaluator noted that dose reductions and interruptions were frequent and are necessary to ameliorate AEs associated with cabozantinib treatment. Most AEs requiring dose modification or interruption occurred early on commencing cabozantinib treatment and the draft PI recommends that patients be closely evaluated over the first 8 weeks of treatment.
- 6.30 The TGA evaluator concluded that the overall safety profile of cabozantinib was consistent with that of VEGFR-TKIs.

#### Indirect comparison of cabozantinib and nivolumab

- 6.31 The safety analysis in METEOR was performed at the May 2015 database cut-off (minimum duration of follow-up 5.9 months in the ITT population). At this time, 40% of patients in the cabozantinib arm and 21% in the everolimus arm remained on treatment. The minimum duration of follow-up in CheckMate 025 was 14 months; 17% of patients in the nivolumab arm and 7% of patients in the everolimus arm remained on treatment. The comparison of safety outcomes across the trials was likely to be confounded by the difference in the duration of follow-up between the two trials.

- 6.32 In the comparison of ‘any AE’ the submission compared the all-cause AEs from METEOR with the treatment-related AEs from CheckMate 025. Similarly, for the comparison of ‘any SAE’, the submission compared all-cause SAEs from METEOR with treatment-related Grade 3-4 AEs from CheckMate 025. Comparisons between the comparable safety outcomes in each trial were performed during the evaluation. The results of the indirect comparison of safety outcomes are summarised in Table 8.

**Table 8: Indirect comparison of safety outcomes: cabozantinib vs nivolumab**

	Intervention n/N (%)	Everolimus n/N (%)	Indirect RR (95% CI)	Indirect OR (95% CI)
<b>Treatment-related AE</b>				
METEOR*	322/331 (97.3%)	293/322 (91.0%)	<b>1.20 (1.11, 1.29)</b>	<b>7.02 (2.99, 16.5)</b>
CheckMate 025**	319/406 (78.6%)	349/397 (87.9%)		
<b>SAE, any causality<sup>a</sup></b>				
METEOR*	131/331 (39.6%)	139/322 (43.2%)	0.84 (0.66, 1.06)	0.73 (0.48, 1.11)
CheckMate 025**	194/406 (47.8%)	173/397 (43.6%)		
<b>Treatment-related Grade 3-4 AE</b>				
METEOR*	195/331 (58.9%)	131/322 (40.7%)	<b>2.83 (2.12, 3.77)</b>	<b>5.22 (3.33, 8.18)</b>
CheckMate 025**	76/406 (18.7%)	145/397 (36.5%)		
<b>Discontinuation due to AE</b>				
METEOR*	34/331 (10%)	31/322 (9.6%)	1.83 (0.98, 3.42)	1.96 (0.98, 3.92)
CheckMate 025**	31/406 (7.6%)	52/397 (13.1%)		

AE = adverse event; CI = confidence interval; OR = odds ratio; RR = relative risk; SAE = serious adverse event

<sup>a</sup> Treatment-related SAEs were not reported for CheckMate 025.

\* METEOR: Minimum duration of follow-up in the ITT population 5.9 months. Median exposure to study drug: cabozantinib 7.6 months, everolimus 4.4 months.

\*\* CheckMate 025: Minimum duration of follow-up 14 months. Median exposure to study drug: nivolumab 5.5 months, everolimus 3.7 months.

Source: Table 2-26 p125, Table 2-34 p132, Table 2-47 p141, Table 2-48 p141, Table 2-50 p142 and Table 2-52 p 144 of the submission.

- 6.33 There was no statistically significant difference between cabozantinib and nivolumab in the number of patients experiencing an AE of any causality, a Grade 3-4 AE of any causality, or the proportion of patients discontinuing treatment due to an AE.
- 6.34 The submission stated that the odds of a SAE were estimated to be higher for cabozantinib than nivolumab, with a 95% CI for the odds ratio of 1.4 to 3.4 and a reasonable degree of precision. This statement was based on the comparison of SAEs of any causality in METEOR and treatment-related Grade 3-4 AEs from CheckMate 025 presented in the submission. There was no significant difference in the rate of SAEs of any causality between cabozantinib and nivolumab. However, the indirect comparison indicated that the odds of experiencing a treatment-related AE of any grade, and of experiencing a treatment-related Grade 3-4 AE, may be higher with cabozantinib than with nivolumab.
- 6.35 The submission concluded that, generally, the results of the indirect comparisons of safety outcomes suggested that cabozantinib was inferior to nivolumab in terms of safety. Given the differences in mechanism of action, and the nature of the comparison presented, the ESC agreed that it was difficult to draw any firm conclusions regarding the comparative safety of the two drugs.

## **Benefits and harms**

- 6.36 Given that nivolumab was considered the most appropriate comparator for cabozantinib, the summary of benefits and harms against everolimus has not been presented here.
- 6.37 A summary of the comparative benefits and harms for cabozantinib versus nivolumab derived from the indirect comparison has not been presented, given the submission did not claim superiority in terms of OS, RECIST-defined PFS is not considered to be a reliable measure of treatment effectiveness for immunotherapies, and the safety data are confounded by the difference in the duration of follow-up in the two trials.

## **Interpretation of clinical evidence**

### Indirect comparison of cabozantinib and nivolumab

- 6.38 The submission claimed that cabozantinib is superior in terms of PFS, non-inferior in terms of OS and ORR, and inferior in terms of safety compared to nivolumab.
- 6.39 The therapeutic conclusion presented in the submission regarding the comparative effectiveness of cabozantinib and nivolumab was not well supported by the evidence presented in the submission:
- As RECIST-defined PFS is not a reliable measure of the clinical effectiveness of nivolumab, the indirect comparison of PFS for cabozantinib compared with nivolumab is of limited clinical relevance. The ESC noted the discussion in the PSCR (p2, p4) around progression and PFS, agreeing that PFS is clinically important and that a delay in progression is likely to have “significant impacts to the patient’s activities of daily living and quality of life”. However, the ESC remained of the view that PFS, as determined by RECIST, was not a reliable outcome for the purpose of the efficacy comparison between cabozantinib and nivolumab, and determination of the relative cost-effectiveness of cabozantinib in the context of the PBS. The ESC agreed with the commentary that the most relevant data for the comparison was the indirect comparison of OS;
  - The indirect comparison for the key patient relevant outcome of OS, lacked the statistical power to rule out a clinically meaningful difference in survival between patients receiving cabozantinib or nivolumab. The ESC noted the CIs around the OS estimates were wide, and that there were differences between the comparator arms used in the indirect comparison;
  - The ESC considered that it was difficult to draw any firm conclusions regarding the comparative safety of cabozantinib and nivolumab given the available information and their distinctly different safety profiles;
  - There are methodological concerns regarding the indirect comparison:
    - The claim was based on an indirect comparison with potential for confounding due to imbalances in unobserved prognostic factors or treatment effect modifiers across the studies, or undocumented differences in study conduct;

- The submission did not specify a non-inferiority margin for any of the outcomes included in the indirect comparison; and
  - The extent of bias resulting from the early analysis of the OS data in each trial, and the resulting direction and extent of bias in the indirectly derived HR, was uncertain.
- 6.40 The PBAC considered that the claim of superior comparative effectiveness over nivolumab in terms of PFS was not adequately supported by the data, as the committee agreed with the ESC that RECIST-defined PFS did not provide the most appropriate basis for the comparison between cabozantinib and nivolumab.
- 6.41 The PBAC considered that the claim of non-inferior comparative effectiveness with nivolumab on the basis of OS was reasonable.
- 6.42 The PBAC considered that the claim of inferior comparative safety with nivolumab was reasonable.

#### Cabozantinib versus everolimus

- 6.43 The submission claimed that cabozantinib is superior in terms of comparative effectiveness (PFS, OS and objective response rate) and non-inferior in terms of comparative safety over everolimus for the treatment of adult patients with clear cell variant RCC whose disease has progressed following prior TKI therapy.
- 6.44 The therapeutic conclusion presented in the submission regarding the comparative effectiveness of cabozantinib and everolimus was reasonable. However, the extent of OS benefit observed at the unplanned interim analysis in METEOR may have overestimated the degree of OS gain, given that the OS data were still relatively immature, and the PBAC has previously considered that hazard ratios tend to become less favourable over time (paragraph 7.7, 6.03 nivolumab Public Summary Document, July 2016 PBAC meeting).
- 6.45 The claim that cabozantinib was non-inferior to everolimus in terms of safety was not well supported, given:
- A greater proportion of patients receiving cabozantinib experienced at least one Grade 3-4 AE (59%) compared to patients receiving everolimus (41%), although the ESC noted that patients in the cabozantinib arm had a higher duration of exposure to treatment than the patients receiving everolimus; and
  - The proportion of patients who required at least one dose reduction due to an AE was considerably higher in patients receiving cabozantinib (60%) compared to those receiving everolimus (24%).
- 6.46 The PBAC considered that the claim of superior comparative effectiveness and non-inferior safety versus everolimus was reasonable.

#### ***Economic analysis***

- 6.47 The submission presented three economic evaluations:
- Two cost-utility analyses:
    - Cabozantinib vs everolimus; and
    - Cabozantinib vs nivolumab.

- A cost-minimisation analysis of cabozantinib vs nivolumab.

6.48 As highlighted above, given its recent PBS listing, nivolumab is considered the most relevant comparator. The ESC considered that the evidence presented to support the superiority claim for cabozantinib vs nivolumab did not provide a reliable basis for a cost-effectiveness model. Therefore, the cost-minimisation approach was the most appropriate.

#### Cost-minimisation analysis vs nivolumab

6.49 The submission estimated the equi-effective doses as cabozantinib 45.15mg daily and nivolumab 240.6mg (80.2kg x 3mg/kg) every 14 days, assuming equal treatment durations.

6.50 The average dose of cabozantinib was based on METEOR, while the average dose of nivolumab is based on the protocol dose in CheckMate 025 (3mg/kg every 14 days), using the average weight of patients in the METEOR trial. While dose-reductions of nivolumab were not allowed in CheckMate 025, a total of 207 of 406 patients treated with nivolumab (51%) had dose delays. The assumption that patients will receive 100% of the schedule dose is inappropriate and will bias the results of the cost-minimisation analysis in favour of cabozantinib.

6.51 The submission stated that in both METEOR and CheckMate 025, treatment was provided until disease progression, occurrence of an adverse event that necessitated discontinuation or until treatment no longer provided clinical benefit (as determined by the investigator). Therefore, the equi-effective doses were estimated assuming both agents are provided indefinitely, while still indicated, assuming equal treatment durations. The assumption of equal treatment duration in the cost-minimisation analysis was unlikely to be appropriate. The ESC considered that using the median treatment durations from METEOR for cabozantinib and CheckMate 025 for nivolumab would be more appropriate.

6.52 The cost-minimisation analysis included costs associated with administration, and those related to the treatment of severe adverse events.

6.53 Results of the cost-minimisation analysis are provided in the table below.

**Table 9: Cost-minimisation analysis at the list price, assuming equal treatment durations**

Once daily cabozantinib at 45.15mg (for 14 days) is equivalent to nivolumab every 14 days at a dose of 3mg/kg			
Ex-manufacturer price for nivolumab		Ex-manufacturer price for cabozantinib	
40mg/4mL, 1x4mL vial	\$830.70	60/40/20mg, 30 tablets	\$ [REDACTED]
100mg/10mL 1x10mL vial	\$2,076.75		
40mg/4mL, 1x4mL vial Plus AHI Fee	\$857.01	DPMQ 60/40/20mg, 30 tablets	\$ [REDACTED]
100mg/10mL, 1x10mL vial Plus AHI fee	\$2,146.68		
Target dose	240.6mg [3 x 80.2kg]		
Drug cost every 14 days	\$5,263.36†	Daily cost of therapy	\$ [REDACTED]
Administration every 14 days	\$97.95	Administration	\$0.00
SAE over 14 days	\$8.95	Daily cost of SAE	\$ [REDACTED]
		Total cost per day	\$ [REDACTED]
Total Cost (over 14 days)	\$5,370.26	Total Cost (over 14 days)	\$ [REDACTED]
Cabozantinib is cost-saving by \$ [REDACTED] every 14 days, or saves the PBS \$ [REDACTED] per day (at the list price)			

SAE = serious adverse event; DPMQ = dispensed price per maximum quantity; AHI = administration, handling and infrastructure;

† a distribution, diluent, preparation and ready prepared dispensing fee was added

Source: Table 3-46, Section 3[B] of the submission.

### Cost-Utility Analysis vs everolimus

6.54 The submission presented a partitioned survival model, with three mutually-exclusive health states: progression-free/stable disease, post-progressive disease and death.

6.55 A summary of the model structure and rationale is provided in the table below.

**Table 10: Summary of the model structure**

Component	Description
Type(s) of analysis	Cost-utility analysis and cost-effectiveness analyses
Outcomes	Cost per QALY gained and cost per LY gained
Time horizon	5 years (10 years in sensitivity analysis)
Method(s) used to generate results	Markov model (partitioned survival model)
Health states	Stable disease, progressive disease, death. Time to treatment discontinuation (TTD) also modelled to account for the costing of study treatments.
Cycle length	Four weeks (28 days), half cycle corrected
Transition probabilities	The submission stated that survival curves for PFS and OS estimates from METEOR trial individual patient data were used. However, the submission applied the parametric curves based on this data for the entirety of the time horizon. Time to treatment discontinuation estimates applied to determine treatment-related costs and adverse events for the cabozantinib and everolimus arms.
Quality of life	Based on EQ-5D-5L estimates from pooled arms of METEOR (assuming no difference in utilities between treatment arms). Disutility adjustments associated with adverse events based on data from EQ-5D-5L METEOR. Incidence of AEs from METEOR.
Resource utilisation	Based on the available literature, review of published economic models
Post-progression disease costs	Subsequent therapies, based on subsequent therapies as reported in the METEOR trial
Software	Microsoft Excel 2010

OS = overall survival; PFS = progression free survival; IPD = individual patient data; TTD = time to treatment discontinuation; AEs = adverse events; QALY = quality adjusted life years; LY = life years

Source: Table 3-2, Section 3 of the submission

6.56 The base case economic analysis allowed for treatment beyond progression, consistent with the METEOR trial. This is inconsistent with the proposed listing of

cabozantinib and the PBS listing of everolimus, which do not allow use after RECIST-defined progression.

- 6.57 PFS, OS and time to treatment discontinuation (TTD) curves applied in the model were based on a jointly estimated log-logistic parametric function estimated from IPD data from the METEOR trial, for both the cabozantinib and everolimus arms. The choice of parametric function was based on a number of factors, including model fit for the observed data (AIC and BIC), and an assessment of quantile-quantile plots to assess whether a proportional hazards or accelerated failure time models were most appropriate.
- 6.58 Utilities for the progression-free health state, post-progression health state and the disutility associated with adverse events were based on EQ-5D data from the METEOR trial.
- 6.59 Subsequent treatments were determined based on the anti-cancer therapies received in the METEOR trial for the cabozantinib and everolimus arms. The question used to derive the data was unclear in the paper and accompanying appendix (Choueiri et al, 2016) and therefore the ESC considered that it was not possible to ascertain if the translation was appropriate. The submission has incorrectly and unreasonably assumed that patients will receive active treatment for each subsequent cycle (until death), and the ESC considered that it was unlikely that this reflected the Choueiri et al data reasonably. Additionally, an average of 12% of patients in the everolimus arm received two (concurrent) active systemic therapies in each cycle until they die (i.e. the number of subsequent treatments received was greater than the number of patients).
- 6.60 The key drivers of the model as they relate to the comparison of cabozantinib vs everolimus are provided in the table below.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact
Subsequent therapy costs	The submission assumed that all patients will receive an active treatment upon progression until death and that the composition of treatments will mirror those in the METEOR trial. The model is also sensitive to the issue that the number of (concurrent) subsequent active anti-cancer therapies received was more than the number of patients alive (eg 12% of patients received 2 concurrent active anti-cancer therapies).	High, favours cabozantinib
Method of extrapolation: choice in parametric function	The submission used the jointly estimated log-logistic function to model PFS, OS and TTD in the submission base case.	Moderate, favours for or against cabozantinib depending on parametric function

PFS = progression free survival; OS = overall survival; TTD = time to treatment discontinuation

Source: Compiled during the evaluation based on information presented in '9.Cabozantinib Section 3 PBAC economic evaluation.xlsx'

- 6.61 The results of the economic evaluation for the comparison of cabozantinib vs everolimus are provided below

**Table 12: Incremental cost-effectiveness ratio for cabozantinib vs everolimus (five-year time horizon)**

	Cabozantinib	Everolimus	Incremental
Life Years	2.37	1.92	0.45
QALYs	1.64	1.33	0.31
Total Costs	\$ [REDACTED]	\$128,503	\$ [REDACTED]
ICER (cost per LYG)			\$ [REDACTED]
ICER (cost per QALY gained)			\$ [REDACTED]

ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years

Source: Table 3-35, Section 3[A] of the submission

The redacted table above shows an incremental cost of cabozantinib compared to everolimus of \$105,000 - \$200,000 per life year gained and more than \$200,000 per QALY gained.

### Cost-Utility Analysis vs nivolumab

6.62 The results of the economic evaluation for the comparison of cabozantinib vs nivolumab are provided below.

**Table 13: Incremental cost-effectiveness ratio for cabozantinib versus nivolumab (five-year time horizon)**

	Cabozantinib	Nivolumab	Incremental
Life Years	2.37	2.27	0.11
QALYs	1.64	1.56	0.08
Total Costs	\$ [REDACTED]	\$196,100	\$ [REDACTED]
ICER (cost per LYG)			\$ [REDACTED]
ICER (cost per QALY gained)			\$ [REDACTED]

Source: Table 3-40, Section 3[A] of the submission

The redacted table above shows a cost of cabozantinib compared to nivolumab of \$45,000 - \$75,000 per QALY gained and per life year gained.

6.63 The submission modelled an average overall survival benefit of 0.107 years (approximately 1.3 months; 2.374 years vs 2.267 years in cabozantinib and nivolumab arm respectively), despite presenting a clinical claim of non-inferiority of cabozantinib vs nivolumab in terms of overall survival. The non-significant point estimates of HR from the indirect comparison for both OS (0.93) and PFS (0.59) were used in the model without considering wide confidence intervals.

### **Drug cost/patient/course: \$ [REDACTED]**

6.64 This calculation is based on the economic evaluation presented in the submission, assuming a cost per 28 days of \$ [REDACTED], and an average treatment duration of approximately 11.2 months (as determined by the mean time spent in the pre-progression health state). Assuming equal treatment durations as per the submission's cost-minimisation analysis the cost/patient/course for the main comparator, nivolumab, is \$128,220. However, there is no evidence for the treatment duration of nivolumab. If the duration of nivolumab in clinical practice is shorter than that for cabozantinib, the cost of cabozantinib per treatment course per patient would be higher than that for nivolumab.

### **Estimated PBS usage & financial implications**

6.65 This submission was not considered by DUSC.

- 6.66 The submission used a market share approach, based on Medicare Australia PBS/RPBS item reports, to estimate the use and financial impact of listing cabozantinib on the PBS for the treatment of patients with Stage IV clear cell variant RCC following first-line treatment with a TKI. The submission assumed that listing of cabozantinib would not alter the estimated total second- and later-line market for treatment of Stage IV clear cell variant RCC. However, as cabozantinib and nivolumab are recommended in preference to other available second- and later-line treatment options, it is likely that cabozantinib will be used sequentially with, rather than substituting for, nivolumab, increasing the overall second- and later-line market. Based on the results of METEOR and CheckMate 025, over 50% of patients in these studies received further systemic treatment subsequent to treatment with nivolumab or cabozantinib. The evaluation considered it was unclear what proportion of patients would use nivolumab and cabozantinib sequentially in clinical practice.
- 6.67 The submission derived the recent utilisation of second-and later-line therapies by calculating the combined number of monthly PBS services for sunitinib and pazopanib, and then assuming that the total utilisation of second-line treatments would be 80% of the total first-line services, based on the assumption that 80% of patients treated with a first-line TKI would be eligible for second-line treatment.
- 6.68 The assumption that 80% of patients treated with first-line sunitinib or pazopanib would be eligible for a second-line treatment was sourced from the previous submission for nivolumab for treatment of RCC. The PBAC noted at that time that recent PBS data indicated that approximately 16.0% (in 2013) to 24.8% (in 2014) of patients initiating on a TKI for RCC went on to be prescribed a second-line therapy, which suggested that the nivolumab submission's assumed uptakes (of 80% for current second-line therapy and 90% for nivolumab once listed) were substantial overestimates (paragraph 7.11, 6.03 nivolumab PSD, July 2016 PBAC meeting).
- 6.69 The market share of everolimus, axitinib and sorafenib, in the absence of nivolumab and cabozantinib, was determined from PBS item reports. The total number of second-line services per month, derived by the method outlined above, was considerably higher than the combined number of services for everolimus, axitinib and sorafenib per month. The submission assumed that the balance was accounted for by the use of 'off-PBS' therapies.
- 6.70 The market share of everolimus, sorafenib and 'off-PBS' treatments, were extrapolated over the first six years of listing. As the extrapolation of axitinib resulted in market share estimates over 100%, the market share of axitinib was assumed to be the residual of all other agents and 'off-PBS' treatment use. Given the limited data on which these extrapolations were based, and the marked changes in the market due to listing of new treatments, these projections were highly uncertain.
- 6.71 The submission assumed that, with listing on the PBS and in the absence of cabozantinib, nivolumab would account for ■■■% of the second- and later-line market. Cabozantinib was subsequently assumed to gain 17% market share in the first year of listing, increasing to ■■■% in Years 4-6. No justification was given for these assumed uptake rates. The balance of the market was assumed to be

distributed between the alternative treatment options in the same proportions as in the absence of cabozantinib.

- 6.72 The submission calculated a single average prescription equivalence rate between cabozantinib and all other therapies for the respective PBS and RPBS settings, for each year of the analysis.
- 6.73 The submission used the number of prescriptions per year to calculate the average prescription equivalence rate, implicitly assuming that the mean duration of treatment with each alternative therapy was the same. As discussed in the economics section of the evaluation, this is not appropriate. The assumption of a similar duration of treatment is likely to have overestimated the cost-offsets resulting from substitution for other drugs.
- 6.74 The submission’s estimate of the net financial impact of listing cabozantinib for the PBS/RPBS is summarised in Table 14. All pharmaceutical costs were based on the published prices.

**Table 14: Financial impact allowing for some sequential use of cabozantinib and nivolumab**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Submission: per the Cabozantinib Section 4 model						
Cost of cabozantinib	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost offsets	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
With sequential use of cabozantinib in poor risk patients (based on METEOR population 12.8%)						
Cost offsets	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
With sequential use of cabozantinib in poor risk patients (based on METEOR population 15.4%)						
Cost offsets	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 5, p5 of the Sponsor’s Pre-PBAC response.

*The redacted table above shows the estimated net cost to the PBS/RPBS for cabozantinib of less than \$10 million per year.*

- 6.75 The evaluation considered there is potential for the net cost/year for the PBS/RPBS to be either greater than or less than the estimate in the submission given that:
  - The submission assumed that listing of cabozantinib would not alter the estimated utilisation of second- and later-line treatments. However, if cabozantinib is used sequentially with nivolumab to a greater extent than predicted by the estimates, rather than substituting for it:
    - The total second- and later-line market for treatment of Stage IV clear cell variant RCC is likely to increase; and

- The submission's estimates of the cost-offsets resulting from substitution for nivolumab, which represented approximately 80% of the estimated total cost offsets, are unlikely to be fully realised.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended listing cabozantinib for the treatment of Stage IV clear cell variant renal cell carcinoma, on a cost-minimisation basis against nivolumab. The PBAC considered that cabozantinib had non-inferior efficacy compared to nivolumab and whilst there was possibly increased toxicity associated, this was manageable and balanced against a clinical need for an alternative to immunotherapy in this patient population.
- 7.2 The PBAC considered that the cost-minimisation should be calculated on the basis that the average cost per patient for cabozantinib is the same as that for nivolumab. The PBAC noted the submission's proposal to calculate the cost-minimisation on the assumption of equal treatment duration for cabozantinib and nivolumab, but considered that this approach was not well supported and favoured cabozantinib. The PBAC recommended that in the absence of further directly comparable data the most appropriate approach for the cost-minimisation would be to use the median durations of each treatment from the METEOR and Checkmate 025 studies.
- 7.3 The PBAC noted that nivolumab, which was presented in the submission as a near to market comparator, had been listed for this patient population in the time since the submission was lodged, and agreed that this was now the most relevant main comparator.
- 7.4 The PBAC considered that, for patients with clear cell variant metastatic RCC, the appropriate clinical place in therapy for cabozantinib would be as a second line alternative to nivolumab in patients who have failed treatment with a TKI, however acknowledged cabozantinib would also be used as third line therapy following second line nivolumab.
- 7.5 The PBAC noted that the restriction for nivolumab includes use in both patients who have failed treatment with a TKI and patients who "have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal." Given the likelihood of patients who have developed an intolerance to first line TKIs also having tolerability issues with cabozantinib, the PBAC did not think this criterion would be appropriate to include in the cabozantinib restriction.
- 7.6 The clinical claim against nivolumab was based on an indirect comparison of two open-label randomised controlled trials comparing cabozantinib and nivolumab with everolimus (METEOR and CheckMate 025, respectively). The PBAC noted that there was considerable uncertainty around the results of the comparison, given its indirect nature, as well as the risk of bias associated with both studies being open-label. The PBAC also noted the ESC's concerns around the lack of statistical support provided for the comparison.
- 7.7 The PBAC noted the discussion in the submission and sponsor responses around the importance of PFS for patients with RCC, but agreed with the ESC that this outcome

did not provide an appropriate basis to support the claim of superior efficacy of cabozantinib over nivolumab. Therefore, the PBAC was of the view that the claim of non-inferior efficacy, based on OS, was the most relevant comparison for determining the cost-effectiveness of cabozantinib for listing on the PBS.

- 7.8 The PBAC noted that there were some differences in the safety profiles, and that the submission had claimed inferior safety. Overall, the PBAC considered that any increased toxicity was likely to be manageable for the majority of patients.
- 7.9 The PBAC considered that cabozantinib was non-inferior to nivolumab in terms of efficacy, and that the cost minimisation approach was appropriate. The PBAC considered that it was appropriate to use different durations of use in calculating the cost-minimisation analysis, as described above (paragraph 7.2).
- 7.10 The PBAC noted that the submission estimated uptake of cabozantinib would represent a ■■■% share of the second-line market, and considered this to be reasonable.
- 7.11 However, the PBAC considered that the financial impact of listing cabozantinib remained uncertain. The PBAC considered that PBS listing of cabozantinib would result in sequential use of cabozantinib and nivolumab, and were of the view that this had not been adequately addressed in the submission. The PBAC acknowledged that re-estimated financial implications were provided in the PSCR to account for sequential use in approximately 15% of patients, but considered that the extent of sequential use was likely to be higher than this, effectively growing the second and later line market at significant additional cost to Government. The PBAC considered that it would be appropriate for the Department to establish a new risk sharing arrangement for cabozantinib, where use is capped at ■■■% of the agreed market for this population, with a 100% rebate over the set cap to manage the risk of additional cost associated with sequential use.
- 7.12 The submission requested flat pricing across the three strengths of cabozantinib. The PBAC noted that patients may receive prescriptions of varying strengths to assist with dose titration, and this may impact the overall cost of cabozantinib to the PBS.
- 7.13 The PBAC advised that cabozantinib is not suitable for prescribing by nurse practitioners, as antineoplastic agents are currently out of scope.
- 7.14 The PBAC recommended that cabozantinib should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.15 The PBAC recommended that the Early Supply Rule should apply.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
CABOZANTINIB			Cabometyx	Ipsen Australia Pty Ltd
Cabozantinib, 60 mg tablet, 30	30	2		
Cabozantinib, 40 mg tablet, 30	30	2		
Cabozantinib, 20 mg tablet, 30	30	2		

<b>Category / program</b>	General Schedule
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	Stage IV
<b>Condition:</b>	Clear cell variant renal cell carcinoma (RCC)
<b>PBS Indication:</b>	Stage IV clear cell variant renal cell carcinoma (RCC)
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	-
<b>Clinical criteria:</b>	Patient must have progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) following first line treatment with a Tyrosine Kinase Inhibitor (TKI); AND Patient must have disease which is WHO performance status of 2 or less; AND Treatment must be the sole PBS-subsidised therapy for this condition
<b>Population criteria:</b>	-
<b>Prescriber Instructions</b>	-
<b>Administrative Advice</b>	-
<b>Definitions</b>	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.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
CABOZANTINIB			Cabometyx Ipsen Australia Pty Ltd
Cabozantinib, 60 mg tablet, 30	30	5	
Cabozantinib, 40 mg tablet, 30	30	5	
Cabozantinib, 20 mg tablet, 30	30	5	

<b>Category / program</b>	General Schedule
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	Stage IV
<b>Condition:</b>	Clear cell variant renal cell carcinoma (RCC)
<b>PBS Indication:</b>	Stage IV clear cell variant renal cell carcinoma (RCC)
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	-
<b>Clinical criteria:</b>	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have stable or responding disease according to the Response Evaluation Criteria in Solid Tumours (RECIST), AND Treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.
<b>Population criteria:</b>	-
<b>Prescriber Instructions</b>	-
<b>Administrative Advice</b>	-
<b>Definitions</b>	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.

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **10 Sponsor's Comment**

For Australians with advanced clear-cell RCC, there is still a serious medical need for access to new treatments that may help to slow progression of the disease, increase the speed at which they derive benefit from treatment and extend overall survival. Ipsen is extremely pleased with the PBAC's decision to positively recommend CABOMETYX (cabozantinib) for listing on the PBS.

Ipsen is committed to working with the Australian Government and the Department of Health over the coming weeks to ensure expedited listing of CABOMETYX (cabozantinib) on the PBS for patients with advanced RCC".