

6.04 CABOZANTINIB, Tablet 20 mg, 40 mg, 60 mg, Cabometyx[®], Ipsen Pty Ltd

1 Purpose of Application

1.1 The submission requested a Section 100, Authority Required (Streamlined), restricted benefit listing for cabozantinib for treatment of patients with Barcelona-Clinic Liver Cancer (BCLC) B or C advanced hepatocellular carcinoma (HCC), WHO performance status ≤ 1 and Child Pugh A disease previously treated with sorafenib.

1.2 The key components of the submission are presented in Table 1.

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

Component	Description
Population	Patients with BCLC stage B or stage C HCC, WHO performance status of 0-1 and Child-Pugh class A risk classification, who have been previously treated with at least one systemic treatment for this condition.
Intervention	Cabozantinib (Cabometyx [®]), 60 mg orally QD until disease progression or unacceptable toxicity.
Comparator	Main comparator: BSC Near market comparator: regorafenib
Outcomes	Overall survival (OS); progression free survival (PFS); objective response rate (ORR); safety
Clinical claim	Cabozantinib provides: <ul style="list-style-type: none"> Significantly superior OS, PFS and ORR compared to standard of care, and a worse but manageable safety profile; No difference of clinical effect between cabozantinib and the possible near market comparator, regorafenib, in terms of OS, PFS, ORR and safety.

Abbreviations: BCLC= Barcelona-Clinic Liver Cancer; HCC= hepatocellular carcinoma; ORR= objective response rate; OS= overall survival; PBS= Pharmaceutical Benefits Scheme; PFS= progression free survival; QD= once daily; WHO= World Health Organization
Source: Table 1-1, p. 18 of the submission.

2 Requested listing

2.1 The submission proposed that a special pricing arrangement (SPA) apply, consistent with the existing PBS listing of cabozantinib for treatment of stage IV clear cell variant renal cell carcinoma (RCC) following prior treatment with a tyrosine kinase inhibitor (TKI). The SPA offered an upfront discount for all packs as specified in the table. The proposed effective DPMQ for cabozantinib was \$ [REDACTED] with a published DPMQ of \$9,951.04 per 30 tablets for all three strengths (60 mg, 40 mg and 20 mg).

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

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
20 MG; Tablet, 30	1	5	\$9,951.04	CABOMETYX Ipsen Pty Ltd
40 MG; Tablet, 30	1	5	published	
60 MG; Tablet, 30	1	2	\$ [REDACTED] effective	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Advanced Barcelona Clinic Liver Cancer stage B or stage C
Condition:	Hepatocellular carcinoma (HCC)
PBS Indication:	HCC in patients who have been previously treated with sorafenib for this condition Advanced Barcelona Clinic Liver Cancer stage B or stage C Hepatocellular carcinoma
Treatment phase:	Initial
Restriction Level / Method:	<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
Clinical criteria:	Patient must have previously received treatment with a tyrosine kinase inhibitor (TKI) for this condition. AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have a WHO performance status of 1 or less, AND Patient must have Child Pugh class A
Population criteria:	Patient must be aged 18 years or older.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
20 MG; Tablet, 30	1	5	\$9,951.04	CABOMETYX Ipsen Pty Ltd
40 MG; Tablet, 30	1	5	published	
60 MG; Tablet, 30	1	2	\$ [REDACTED] effective	

Category / Program	General Schedule (Code GS) GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Advanced Barcelona Clinic Liver Cancer stage B or stage C
Condition:	Hepatocellular carcinoma (HCC)
PBS Indication:	HCC in patients who have been previously treated with sorafenib for this condition Advanced unresectable Barcelona Clinic Liver Cancer stage B or stage C Hepatocellular carcinoma
Treatment phase:	Continuing
Restriction Level / Method:	<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
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have previously received been treated with PBS-subsidised cabozantinib-treatment with this drug for this condition AND Patient must not develop have progressive disease progression while receiving treatment with this drug for this condition.
Population criteria:	Patient must be aged 18 years or older.

2.3 The submission proposed two wordings of the restriction for eligibility to initiate treatment: one stipulated use following sorafenib therapy, the other following prior systemic therapy. The latter was in recognition that lenvatinib had been considered by the PBAC. Lenvatinib was listed for use in the first line setting of HCC on 1 March 2019. CELESTIAL does not provide evidence of the efficacy of cabozantinib post lenvatinib. The Pre-Sub-Committee Response (PSCR) noted that at the time the CELESTIAL trial was conducted only sorafenib was available as the standard of care. The PSCR also noted that subgroup analyses of the CELESTIAL trial showed consistent survival benefit with the whole trial population regardless of prior treatments, though they were not powered to detect a treatment difference. Given that lenvatinib was listed on a cost-minimisation basis with sorafenib, it may be appropriate to adopt the

broader initiation criteria to facilitate physician discretion in prescribing first-line therapy.

- 2.4 In considering regorafenib for advanced HCC at its November 2018 meeting, the PBAC acknowledged that the listing for a therapy in a second-line should not influence the choice of therapies in the first-line setting and accordingly suggested the criterion “following treatment with a tyrosine kinase inhibitor (TKI)” (regorafenib PSD, November 2018, point 7.3). The same wording would be applicable in the case of cabozantinib in the second-line setting. The PBAC agreed with the ESC that despite the lack of evidence post lenvatinib, it would be appropriate to allow clinicians to determine the most appropriate first line TKI for patients prior to cabozantinib. The ESC considered that specifying use subsequent to a TKI rather than a systemic therapy, as proposed in the submission, would better reflect the currently available first-line therapies in HCC and the therapies used in CELESTIAL.
- 2.5 The requested listing specifies that patients have been treated with sorafenib (or at least one systemic therapy) for this condition; however, the wording does not specify whether patients intolerant to sorafenib (or lenvatinib) should be eligible for treatment with cabozantinib under this listing. Patients in the CELESTIAL trial either progressed following at least one systemic therapy (sorafenib) or developed toxicities leading to discontinuation. The PBAC considered the restriction wording should specify that patients treated with cabozantinib are required to have progressed on a first line TKI.
- 2.6 In addition, the proposed restriction does not permit use beyond treatment progression, while in CELESTIAL patients continued treatment beyond progression if the investigator considered they were experiencing clinical benefit. The PBAC agreed with the ESC that use beyond progression would not be appropriate and this should be included in the restrictions as proposed.

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

3 Background

Registration status

- 3.1 Cabozantinib was TGA registered for HCC on 21 May 2019. The full indications are:
- “Renal Cell Carcinoma (RCC)
CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC):
- in treatment-naïve adults with intermediate or poor risk
- in adults following prior treatment with vascular endothelial growth factor targeted therapy.

Hepatocellular Carcinoma (HCC)
CABOMETYX is indicated as monotherapy for the treatment of hepatocellular

carcinoma (HCC) in adults who have previously been treated with sorafenib.”

Previous PBAC consideration

- 3.2 This is the first major submission to the PBAC for cabozantinib in the treatment of advanced HCC.

4 Population and disease

- 4.1 According to the 2019 Australian Institute of Health and Welfare (AIHW) cancer report, the incidence of liver cancer increased more than four-fold (from 1.8 to 8.6 per 100,000 persons) between 1982 and 2019. Indigenous Australians were 2.4 times more likely to be diagnosed with liver cancer compared to non-indigenous Australians. The incidence is likely to continue to rise as a result of current cases of asymptomatic chronic viral hepatitis, immigration from countries with high hepatitis B and C virus (HBV/HCV) prevalence and the steadily increasing incidence of obesity and lifestyle related diseases that contribute to HCC. Primary liver cancer is also the fastest increasing cause of cancer death, and five-year survival in Australia remains poor, at 16%.
- 4.2 Cabozantinib is proposed as a second/third-line treatment of patients who previously progressed on sorafenib or, alternatively, systemic therapy. The alternative proposed restriction should be specific for use following treatment with a TKI.

5 Comparator

- 5.1 The submission nominated BSC as the main comparator. The ESC agreed with the evaluator that this was appropriate. The submission included a secondary indirect treatment comparison (ITC) with regorafenib, as a possible near market comparator. Regorafenib has been rejected twice by the PBAC based on a high incremental cost-effectiveness ratio (ICER) and inferior safety (regorafenib PSD, March 2018, point 7.1; regorafenib PSD, November 2018, point 7.1).
- 5.2 The submission excluded nivolumab (TGA registered) as a relevant comparator on the basis that the registered indication was granted based on a single-arm study that presented objective response rates (ORR) and duration of response, with no evidence of improvements in OS or disease-related symptoms. The exclusion of a potentially relevant comparator based on the evidence available is not appropriate. Nonetheless, as nivolumab is not PBS listed for HCC and has not yet been considered for listing in HCC, the evaluator considered its exclusion was appropriate.
- 5.3 The PBAC considered that given no other therapy is listed for second-line treatment, the submission appropriately used BSC as the main comparator, with regorafenib as a secondary “near-market” comparator.

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 that no consumer comments were received for this item.

6.3 The Medical Oncology Group of Australia (MOGA) expressed its support for the cabozantinib in advanced HCC submission, categorising it as one of the therapies of “other supported applications” on the basis of the CELESTIAL trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for cabozantinib in advanced HCC, 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 BSC.

Clinical trials

6.4 The submission presented a primary comparison of cabozantinib with BSC (informed by CELESTIAL, n=707), which is a Phase 3, randomised, double blind, placebo-controlled study of cabozantinib in patients with HCC who have received prior sorafenib.

6.5 The ITC of cabozantinib against regorafenib was informed by the RESORCE trial (n=573), with BSC as the common reference. RESORCE is a Phase 3, randomised, double blind, placebo-controlled study of regorafenib in patients with HCC who have received prior sorafenib.

6.6 Details of the trials presented in the submission are provided in Table 2.

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.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CELESTIAL	<p>Clinical study report – second interim analysis</p> <p>Statistical Analysis Plan - version 2</p> <p>Abou-Alfa GK, Meyer T, Cheng AL et al. "Cabozantinib versus placebo in patients with advanced hepatocellular carcinoma who have received prior sorafenib: Results from the randomized phase 3 CELESTIAL trial.</p> <p>Abou-Alfa GK, Cheng AL, Meyer T et al. 2014. "Phase 3 randomized, double-blind, controlled study of cabozantinib (XL184) versus placebo in patients with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL; NCT01908426)."</p> <p>Abou-Alfa GK, Cheng, AL, Meyer T et al. Phase 3 randomized, double-blind, controlled study of cabozantinib (XL184) versus placebo in patients with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL; NCT01908426).</p> <p>Abou-Alfa GK, Meyer T, Cheng AL et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma.</p>	<p>Data cutoff date: 1 June 2018 (report date 8 February 2018)</p> <p>8 June 2016</p> <p>Gastrointestinal Cancers Symposium 2018; San Francisco, CA, 18–20 January,</p> <p>Journal of Clinical Oncology 2014; 32 (15 SUPPL. 1).</p> <p>Journal of clinical oncology 2015; 33 (3 suppl. 1).</p> <p>New England Journal of Medicine 2018, 379(1), 54-63.</p>
RESORCE	<p>Bruix, J., Finn, RS, Kudo, M. et al. RESORCE: an ongoing randomized, double-blind, phase III trial of regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing on sorafenib (SOR).</p> <p>Solms, A., Reinecke, I., Fiala-Buskies, S. et al. "Exposure-response relationship of regorafenib efficacy in patients with hepatocellular carcinoma." http://dx.doi.org/10.1016/j.ejps.2017.05.050.</p> <p>Bruix, J., Qin, S., Merle, P. et al. "Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial."</p> <p>Anonymous. Erratum: regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial</p> <p>Finn, R. S., Merle, P., Granito, A. et al. "Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial."</p>	<p>Journal of clinical oncology 2014; 32 (15 suppl. 1).</p> <p>European Journal of Pharmaceutical Sciences 2017; 109 (Supplement): S149-S153.</p> <p>The Lancet 2017; 389 (10064):56-66.</p> <p>The Lancet 2017; 389 (10064):36.</p> <p>J Hepatology 2018; 69 (2), 353-358.</p>

Source: Table 2-2, P. 48 of the submission.

6.7 The key features of the CELESTIAL and RESORCE trials are summarised in Table 3.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Cabozantinib vs. BSC						
Abou-Alfa 2018	707	R, DB, MC 22.9 m	Low	Progressed on sorafenib	OS, PFS, ORR	OS, PFS
Regorafenib vs. BSC						
Bruix 2017	573	R, DB, MC 33 months	Low	Progressed on ^a and tolerant ^b to sorafenib.	OS, PFS, ORR	Not used

Abbreviations: BSC= best supportive care; DB= double blind; MC= multi-centre; OL= open label; ORR= objective response rate; OS= overall survival; PFS= progression-free survival; R= randomised.

Note: ^aPatients had to have received their last sorafenib dose within 10 weeks of randomisation. ^bPatients were considered tolerant if they had received sorafenib at a minimum dose of 400 mg/day for more than 20 days.

6.8 Both trial designs had a low risk of bias. CELESTIAL allowed patients to continue treatment beyond progression. Post-progression treatment in the CELESTIAL trial occurred in 20% of patients with an interval of 28 days from documentation of disease progression to treatment discontinuation. The proportion of patients who progressed but were permitted to continue treatment beyond 28 days from disease progression with cabozantinib could not be located within the submission or its supporting documents. The proposed PBS listing limits ongoing therapy to those without progression. The ESC considered that the impact on survival of treatment beyond progression is likely to be minimal.

Comparative effectiveness

Cabozantinib vs. BSC

- 6.9 A significant increase in terms of OS and PFS was observed for cabozantinib compared to BSC.
- 6.10 The estimated OS HR=0.76 (95% CI 0.63, 0.92). The Kaplan-Meier curves for OS (Figure 1) showed that at approximately month 34 the curves converged and cross soon thereafter. At this time point the number of patients at risk was very low, complicating the interpretation of any OS difference after that point.
- 6.11 The results for CELESTIAL showed a difference in PFS in favour of cabozantinib with HR=0.44 (95% CI 0.36, 0.52). The primary analysis for PFS showed that patients treated with cabozantinib were more likely to die without progressing compared to BSC (14% versus 8% respectively), but the difference was not statistically significant.
- 6.12 The results for OS and PFS in CELESTIAL are shown in Table 4. The Kaplan-Meier plot for OS is shown in Figure 1.

Table 4: Results of OS and PFS in CELESTIAL

	Cabozantinib		BSC		Difference in median, months (95% CI)	P value (log rank test)	Hazard ratio (95% CI)
	n/N with event (%)	Median time to event (95% CI)	n/N with event (%)	Median time to event (95% CI)			
PFS	349/470 (74.3%)	5.2 (4.0, 5.5)	205/237 (86.5%)	1.9 (1.9, 1.9)	3.3 (2.1, 3.6)	p<0.0001	0.44 (0.36, 0.52)
OS	317/470 (67%)	10.2 (9.1, 12.0)	167/237 (70%)	8.0 (6.8, 9.4)	2.2 (2.3, 2.6)	p=0.0049	0.76 (0.63, 0.92]

Abbreviations: BSC= best supportive care; CI= confidence interval; n= number of participants reporting data; N= total participants in group; OS= overall survival; PFS= progression free survival.

Source: Table 2-11, 2-12, 2-15, 2-16, p. 74-75 and 82-84 of the submission.

lead to differences in the baseline capacity of the two patient groups to benefit from subsequent therapy.

- the definition of progression events differed in CELESTIAL compared to RESORCE, which used the RECIST criteria version 1.1 and mRECIST respectively. RESORCE reported PFS using both approaches without noting differences in the outcomes. In addition, in CELESTIAL, the occurrence of clinical progression was not recorded as a progression event for the purpose of assessing PFS as compared to RESORCE. It is unclear whether this may have biased the ITC since clinical progression may precede radiographic evidence of disease. However, the relative impact would depend on whether this favourably impacts on cabozantinib more than BSC, thus biasing the indirect comparison with regorafenib.

- 6.16 The hazard ratios (HR) reported for the ITC in the submission were not consistent with the odds ratios (OR) provided in the ITC workbook (Attachment 12 of the submission). The sponsor stated in the Pre-PBAC response (p1) that HR was the preferred measure, and that OR has limited validity and was provided only for transparency and completeness, however HR calculations for the ITC were not provided with the submission. The ITC results indicated that there was no difference in clinical effect between cabozantinib and regorafenib in terms of OS (OR=1.80; 95%CI 1.00, 3.25) however there was some difference in PFS in favour of regorafenib (OR=2.62; 95% CI 1.17, 5.83). In addition, differences were apparent in the magnitudes of the reported outcomes for the control groups in the two studies; 70% versus 87% died and 86% versus 95% progressed in CELESTIAL versus RESORCE, respectively. These differences suggest an underlying issue with the transitivity of the study populations.
- 6.17 The PSCR provided a report for a matching-adjusted indirect comparison (MAIC) of cabozantinib compared with regorafenib to address the transitivity issues identified between the CELESTIAL and RESORCE trials. The MAIC included comparative efficacy and safety considering the pure second-line patients from CELESTIAL (excluding patients who received cabozantinib as third line treatment in CELESTIAL), relative to those in RESORCE. Results were consistent with those in the submission in terms of OS (no statistical differences) but not for PFS where statistical differences were found favouring cabozantinib (HR= 0.715; 95% CI: 0.572, 0.895).
- 6.18 The PBAC considered that the MAIC appeared to support the conclusion of non-inferiority for cabozantinib compared with regorafenib in the population with one prior systemic regimen; however, this comparison has not been independently evaluated as it was provided with the PSCR.

Comparative harms

Cabozantinib vs. BSC

- 6.19 Safety data presented in the submission were obtained from CELESTIAL and are summarised in Table 6. The most frequent Grade 3/4 adverse events (AEs) reported for patients in the cabozantinib arm were palmar-plantar erythrodysesthesia

syndrome (PPES), hypertension, aspartate aminotransferase (AST) increased, fatigue and diarrhoea.

- 6.20 The sponsor stated in the pre-PBAC response (p1-2) that diarrhoea and PPES have long been associated with the antimetabolites used in cancer treatment, and that clinicians in Australia will be reasonably sophisticated in managing these deleterious effects of oncology treatments.
- 6.21 Patients treated with cabozantinib were more likely to experience Grade 3/4 AEs or SAEs compared to BSC and were more likely to experience AEs leading to treatment discontinuations related to study drug compared to BSC. No statistically significant differences were found in the incidence of Grade 5 events in CELESTIAL, however the ESC noted that there were 6 treatment-related deaths (Grade 5 events) in patients treated with cabozantinib compared with 1 in the placebo group.

Table 6: Overview and key AEs (safety population) in CELESTIAL

Type of AE n (%)	Cabozantinib (N = 467)	BSC (N = 237)	RD (95% CI)
Treatment-related AE	439 (94)	148 (62)	0.32 (0.25,0.38)
SAEs	232 (50)	87 (37)	0.13 (0.05,0.21)
Treatment-related SAE	82 (18)	14 (5.9)	0.12 (0.07,0.16)
Worst Grade 3 or 4 AE	316 (68)	86 (36)	0.31 (0.24,0.39)
Worst Grade 4 AE	46 (9.9)	6 (2.5)	0.07 (0.04,0.11)
Worst treatment-related Grade 4 AE	25 (5.4)	3 (1.3)	0.04 (0.02,0.07)
Treatment-related Grade 5 AE	6 (1.3)	1 (0.4)	0.01 (-0.01,0.02)
AE leading to treatment discontinuation ^a	96 (21)	10 (4.2)	0.16 (0.12,0.21)
AE leading to treatment discontinuation ^a related to study treatment	74 (16)	6 (2.5)	0.13 (0.09,0.17)
AE leading to dose modification ^b	416 (89)	94 (40)	0.49 (0.43,0.56)
Diarrhoea	46 (9.9)	4 (1.7)	0.08 (0.05,0.11)
PPES	79 (17)	0	0.17 (0.13,0.20)
Fatigue	49 (10)	10 (4.2)	0.06 (0.03,0.10)
Hypertension	74 (16)	4 (1.7)	0.14 (0.11,0.18)
AST	55 (12)	16 (6.8)	0.05 (0.01,0.09)

Abbreviations: AE= adverse event; AST= aspartate aminotransferase increased; BSC= best supportive care; CI=confidence interval; PPES= palmar-plantar erythrodysesthesia syndrome; RD= risk difference; SAE= serious adverse event.

Source: Table 2-23 and Table 2-24; p. 110 and 112 of the submission. Information was also gathered from the submission to provide information for regorafenib.

Note: bold text indicates statically significant differences; ^a not related to disease progression; ^b defined as dose reduction or interruption.

Cabozantinib vs. regorafenib: ITC

- 6.22 The claim from the submission that cabozantinib was non-inferior to regorafenib in terms of safety was not supported by the ITC presented in the submission. There was a statistically significant higher incidence of SAEs (OR= 1.86; 95% CI: 1.16, 2.99) and discontinuations due to AEs (OR= 4.21; 95% CI: 1.90, 9.34) for cabozantinib compared with regorafenib. The PBAC noted that there was a higher consent withdrawal rate in the RESORCE trial (26% for regorafenib, compared with 11% for cabozantinib in the CELESTIAL trial) and overall the rates of discontinuation were similar. The apparent higher incidence of safety events for cabozantinib may also reflect the underlying transitivity issues between these studies; patients in CELESTIAL may have been more

heavily pre-treated. While there was no statistically significant difference in terms of Grade 5 AEs, there was a trend for cabozantinib being associated with more deaths compared to regorafenib, with the lower end of the confidence interval close to 1 (OR= 1.81; 95% CI: 0.96, 3.44).

- 6.23 No differences were found in the incidence of specific AEs like palmar-plantar erythrodysesthesia syndrome (PPES) (OR= 1.22; 95% CI: 0.53, 2.80) or diarrhoea (OR= 1.27; 95% CI: 0.71, 2.28), the two most commonly observed AEs in CELESTIAL and RESORCE. In the MAIC provided with the PSCR no statistical differences were noted for the most commonly reported AEs, except for diarrhoea (OR= 1.74; 95% CI: 1, 2.48). The MAIC report did not contain information on other relevant safety outcomes like the incidence of serious AEs and AEs related discontinuations, for which differences were reported and the data provided with the PSCR have not been evaluated.

Benefits/harms

Cabozantinib vs. BSC

- 6.24 The comparative benefits and harms for cabozantinib versus BSC are presented in Table 7.

Table 7: Summary of comparative benefits and harms for cabozantinib versus BSC

Benefits						
Progression free survival (median duration of follow up 22.9 months ^a)						
Event	Cabozantinib	BSC	Absolute Difference	HR (95% CI)		
Progressed/dead, n (%)	349/470 (74.3)	205/237 (86.5)	12.2%	0.44 (95% CI 0.36, 0.52) P<0.0001		
% not progressed/alive at 6 months (95% CI)	38.1% (NR)	11.1% (NR)	27%			
% not progressed/alive at 12 months (95% CI)	14.5% (NR)	3.4% (NR)	11.1%			
Overall survival (median duration of follow up 22.9 months)						
Deaths, n/N (%)	317/470 (67)	167/237 (70)	3%	0.76 (95% CI 0.63, 0.92) P=0.0049		
% Alive at 12 months (95% CI)	45.6% (NR)	34.3% (NR)	11.3%			
% Alive at 24 months (95% CI)	17.8% (NR)	12.5% (NR)	5.3%			
Harms						
	Cabo n/N	BSC n/N	RR (95% CI)	Event rate/100 patients ^b		RD (95% CI)
				Cabo	BSC	
Grade 3 and 4 adverse events (≥ 10%)						
Diarrhoea	46/467	4/237	5.84 (2.13, 16.02)	9.9	1.7	0.08 (0.05,0.11)
PPES	79/467	1/237	40.09 (5.61,286.39)	17	0	0.17 (0.13,0.20)
Fatigue	49/467	10/237	2.49 (1.28, 4.82)	10	4.2	0.06 (0.03,0.10)
Hypertension	74/467	4/237	9.39 (3.47,25.37)	16	1.7	0.14 (0.11,0.18)
AST	55/467	16/237	1.74 (1.02, 2.98)	12	6.8	0.05 (0.01,0.09)

Abbreviations: BSC= best supportive care; CI= confidence interval; HR= hazard ratio; NR= not reported; OS= overall survival; PFS= progression free survival.

Source: Table 2-11, 2-12, 2-15, 2-16, p. 74-75 and 82-84 of the submission.

Note: bold text indicates statically significant differences, ^a As the primary efficacy endpoint was met, statistical testing of secondary efficacy endpoints employed the same data cutoff date as the primary analysis of OS; ^b rate reported as per trial duration, 22.9 months.

6.25 On the basis of the direct evidence presented by the submission, for every 100 patients treated with cabozantinib in comparison to BSC:

- Approximately 11 additional patients will be alive at 12 months.
- Approximately 11 additional patients will remain progression free at 12 months.

Over a median duration of follow-up of 22.9 months:

- Approximately 8 more patients will experience diarrhoea.
- Approximately 17 more patients will experience a palmar-plantar erythrodysesthesia (redness/swelling/pain of the hands and feet).
- Approximately 6 more patients will experience fatigue.
- Approximately 14 more patients will experience hypertension (increased blood pressure).
- Approximately 5 more patients will experience increased liver enzymes.

Cabozantinib vs. regorafenib: ITC

6.26 A summary of the comparative benefits and harms is not relevant for the comparison of cabozantinib with regorafenib given the non-inferiority claim.

Clinical claim

Cabozantinib vs. BSC

6.27 The submission claimed that cabozantinib is superior to BSC for the treatment of advanced HCC, providing significantly superior OS, PFS and ORR compared to BSC, and a worse but manageable safety profile. The clinical claim was supported by the evidence. The safety claim is likely to be supported by the evidence from CELESTIAL, noting that the management of Grade 3/4 AEs reported may require interventions beyond dose interruption/reduction. The ESC noted that AEs such as PPES and diarrhoea make this class of drugs difficult to manage.

6.28 The PBAC considered that the claim of superior comparative effectiveness of cabozantinib compared with BSC was reasonable.

6.29 The PBAC considered that the claim of inferior comparative safety of cabozantinib compared with BSC was reasonable. The PBAC noted that the adverse event profile of cabozantinib is not benign, leading to discontinuations, interruptions, and reductions, but the description of “manageable” is still reasonable for the majority of patients, aided by the flexibility in dose. The PBAC noted the TGA comment that safety profile of cabozantinib is not fully characterised in HCC.

Cabozantinib vs. regorafenib: ITC

6.30 The submission claimed non-inferiority for cabozantinib with the near market comparator, regorafenib, in terms of OS, PFS, ORR and safety. The evaluator considered this was reasonable for the efficacy outcomes but not for safety, noting that potential transitivity issues may have biased the analysis against cabozantinib.

The ESC considered, taking into consideration the differences in trial populations, that safety is likely to be comparable between cabozantinib and regorafenib.

- 6.31 The PBAC considered that the claim of non-inferior OS of cabozantinib compared with regorafenib, using BSC as the common reference, was reasonable. The PBAC considered that the claim of non-inferior PFS and ORR compared with regorafenib was not adequately supported by the evidence presented.
- 6.32 The PBAC considered that the claim of non-inferior comparative safety of cabozantinib with regorafenib, using BSC as the common reference, was not adequately supported by the data. The PBAC considered that the safety data were inconclusive, noting that apparent differences in safety events may be because the CELESTIAL trial recruited both second- and third-line patients while the RESORCE trial recruited second-line patients only. The PBAC noted that the rate of diarrhoea is higher for cabozantinib compared with regorafenib using the MAIC analysis, where second-line line cabozantinib patients are compared with second-line regorafenib patients. Overall, the PBAC agreed with ESC that the safety profile of cabozantinib and regorafenib is likely to be comparable in clinical practice.

Economic analysis

- 6.33 The submission presented a cost utility analysis (CUA) comparing cabozantinib with BSC, as outlined in Table 8.

Table 8: Summary of model structure and rationale

Component	Description
Types of analysis	CEA and CUA
Outcomes	Cost per LYG and QALY gained
Time horizon	5 years
Method used to generate results	Partitioned survival model
Health states	Pre-progression, progressive disease and dead
Cycle length	28 days, half cycle corrected
Area under the curve (AUC)	Survival curves for PFS, TTD and OS estimated from CELESTIAL trial IPD.
Health-related quality of life	Calculated from EQ-5D data collected in the clinical trial.
Resource utilisation	Based on the available literature, eviQ and a review of published economic models.
Post-progression disease costs	Subsequent therapies as reported in CELESTIAL.
Software	Microsoft Excel 2010

Abbreviations: AUC= area under the curve; CEA= cost-effectiveness analysis; CUA= cost-utility analysis; EQ-5D= EuroQoL five dimension; HCC= hepatocellular carcinoma cancer; IPD= individual patient data; LYG= life year gained; QALY= quality adjusted life year; PFS= progression free survival; OS= overall survival; TTD= time to treatment discontinuation.

Source: Compiled during the evaluation based on Table 3-2, p157 of the submission.

- 6.34 The submission excluded patients from Asian centres from the base case analysis on the basis that would not reflect practice in Australia. To support this claim, the submission noted that patients from Asian centres had poorer OS outcomes which were likely due to systematic differences in disease and treatment for HCC in these countries where higher rates of mortality were observed. The exclusion of patients from Asian centres from the base case analysis was inappropriate given the ethnicity of the Australian population. At its March 2018 meeting, the PBAC noted that 38% of

patients in RESORCE came from Asian centres (regorafenib PSD, March 2018, point 6.8). However, while the PBAC noted that there were differences between the RESORCE population and the Australian setting due to the strict inclusion criteria in RESORCE, there was no evidence that such a difference had a meaningful impact on the treatment effect (regorafenib PSD, March 2018, point 7.6). The PSCR maintained that the exclusion of patients from Asian centres in the base case was valid and was based on differences in clinical practice rather than the impacts of ethnicity. The PSCR also noted that patients with Asian ethnicity were not excluded from the analysis. The ESC noted that treatments such as TACE (transarterial chemoembolization) are potentially available to patients in Australia. The ESC also noted no treatment by subgroup interactions were presented, and the confidence intervals overlapped with the HR for the ITT population for the various subgroups presented. The ESC considered that the ITT analysis provided the greatest precision (due to sample size) and was the most reliable basis on which to form an estimate of the cost-effectiveness of cabozantinib versus BSC. The sponsor maintained that the base case excluding patients treated in Asian centres best reflects the Australian setting and argued that differences in aetiology (higher proportion of HBV), population (more metastatic disease, younger patients) and treatment (more TACE and NPACT [placebo arm]) in Asia, confound the OS outcome. The PBAC agreed with the ESC that exclusion of Asian centres significantly and unnecessarily reduced the sample size, and the economic model for cabozantinib versus BSC should be based on data from the full ITT population.

- 6.35 The submission extrapolated the observed data from CELESTIAL out to five years. This was despite the data showing that at 24 months, there were approximately 18% of cabozantinib patients and 13% of BSC patients alive, and that beyond that, the OS curves had converged at month 34. The ESC considered that the 5 year time horizon was questionable given the convergence of OS and noted that the curves in the economic model never converged, thus overestimating the OS benefit. The sponsor stated in the pre-PBAC response (p3) that convergence of Kaplan-Meier curves at 34 weeks is an artefact of the low number of patients at risk at 34 weeks in the placebo arm (n=5) and a high rate of censoring in the tails of both KM curves. The sponsor recalculated the base case ICER in the pre-PBAC response (p2) to allow for convergence of the KM curves from month 34 to month 60. The PBAC considered this approach was not appropriate and that the base case should have convergence applied to survival curves starting at the median follow-up of 22.9 months as this better reflects the available data. This resulted in an ICER of \$105,000 - \$200,000 per QALY gained excluding Asian centres, and \$105,000 - \$200,000 per QALY gained for the ITT population.
- 6.36 The submission applied the extrapolated survival data to the entirety of the model time-horizon without including the Kaplan-Meier data. The ESC considered that the Kaplan-Meier data should have been applied to the point of median follow-up. Overall, the approach to the extrapolation of survival outcomes was not well justified

and the criteria used for the selection of the fitted parametric functions was not well described by the submission. The PBAC noted that if Kaplan-Meier data were applied up to the median follow-up, and convergence applied to survival curves starting at the median follow-up of 22.9 months, the ICER increased to \$105,000 - \$200,000 per QALY gained excluding Asian centres, and \$105,000 - \$200,000 per QALY gained for the ITT population. The Sponsor stated in the pre-PBAC response (p2) that extrapolating from the point of median follow-up commences the extrapolation of health outcomes at a point of high uncertainty and argued it would be more appropriate to model each of the Kaplan-Meier curves to their individual median survival and extrapolate from the median onwards. The PBAC considered that the extrapolation method chosen by the sponsor was not well justified.

- 6.37 The economic model included utility values that did not reflect the results from CELESTIAL that showed poorer quality of life for cabozantinib patients. The health outcomes used in the base case of the economic evaluation were obtained from additional analyses comparing several regression models on HRQoL of patients from CELESTIAL. To do the analysis, the submission used the crosswalk method to transform the EQ-5D-5L results from CELESTIAL to EQ-5D-3L values (based on the UK tariff). Regression analyses were applied to the EQ-5D-3L results to take account of the impact on quality of life of treatment status, progression status, TEAE grade and treatment arm. The submission did not justify why it did not apply the HRQoL data obtained directly from CELESTIAL in the economic model rather than using values derived from the regression models. The approaches used in the HRQoL analyses appeared reasonable; however, the selection of the utility values for use in the base case of the economic model was not justified. The model chosen applied a common treatment effect rather than the alternative model, which incorporated the inferior HRQoL of cabozantinib compared with BSC as per CELESTIAL. The evaluator considered this approach would have been preferable; however, the PSCR and pre-PBAC response (p3) argued that this model was not reasonable. The PBAC agreed with the ESC that the utilities used in the base case did not fully capture adverse events and toxicity experienced by patients treated with cabozantinib. The pre-PBAC response (p3) argued that the efficacy and safety of cabozantinib and regorafenib are similar and an alternative set of utility values to apply are those from the RESORCE study, which resulted in an 11% reduction in the ICER. The PBAC considered that applying the utilities from RESORCE may be an appropriate approach.
- 6.38 Post-progression therapies applied in the economic evaluation were obtained from CELESTIAL. As not all post-progression treatments used in CELESTIAL would apply in Australia, the submission assumed that use of the treatments in CELESTIAL would be as per treatment protocols and guidelines published by eviQ. The submission noted that there were some patients who used more than one treatment in CELESTIAL. However, it was unknown what proportion used multiple treatments at the same time or used only one treatment at a time but received multiple lines of subsequent treatment. That is, data on subsequent treatment use were reported in CELESTIAL as

instances of use rather than use per patient. Without accounting for multiple lines of therapy within patients, it is likely that subsequent treatment use has been overestimated. The evaluation tested the sensitivity of the model to this parameter by varying costs by an arbitrary 30% in either direction (for both treatment arms separately and together).

6.39 A summary of the model results based on the cabozantinib proposed effective price is presented in Table 9. Based on the published price, the base case ICER for cabozantinib compared to BSC was estimated at more than \$200,000/QALY gained, compared with \$105,000 - \$200,000/QALY at the proposed effective price.

Table 9: Results of the economic evaluation (effective price)

Component	Proposed medicine	Comparator	Increment
Costs	\$ [REDACTED]	\$20,097	\$ [REDACTED]
QALYs	[REDACTED]	0.70	[REDACTED]
ICER			\$ [REDACTED]

Abbreviations: ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

Source: developed during the evaluation based on the excel model Attachment 13. Only the cost of the proposed medicine was changed to reflect the effective price.

6.40 A summary of the key drivers of the model is presented in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case (ICER = \$ [REDACTED])
Prior therapies	Inclusion of all patients with prior treatments	High, favours cabozantinib (ICER = [REDACTED] post-sorafenib only)
Outcomes	Exclusion of patients from Asian centres	High, favours cabozantinib (ICER = [REDACTED] for ITT)
Extrapolation	Selection of log-logistic function for OS of cabozantinib	High, favours cabozantinib (ICER = [REDACTED] for the Gompertz)
Utilities	Derived from one of several compared regression models	High, favours cabozantinib (ICER = [REDACTED] for the utility values adjusted for treatment arms)

Abbreviations: ICER = incremental cost effectiveness ratio; OS = overall survival

Source: developed during the evaluation based on the excel model Attachment 13.

6.41 A summary of the key sensitivity analyses presented by the submission, re-estimated based on the effective price of cabozantinib, was developed during the evaluation and is presented in Table 11. Additional sensitivity analyses developed during the evaluation relating to the use of alternative utility values, application of the Kaplan-Meier data, alternative extrapolation functions and changes to the estimation of post-progression therapy are also shown in Table 11. Sensitivity analyses have been updated using the full ITT population as considered appropriate by the ESC.

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Table 11: Key results of sensitivity analyses (effective price)

Variable	Base case value (The submission)	Plausible value	Inc. QALYs	Inc. costs	ICER \$/QALY	% ICER change	ICER (ITT)
Base case			0.27			-	
Time horizon	5 years	3 years	0.21			+16%	
Populations and assumptions							
Full CELESTIAL population (ITT)			0.20			+30%	-
Sorafenib only prior treatment			0.17			+38%	-
Utilities estimates	Multivariate mixed model for repeat measurement	Health states: TA514 - Regorafenib	0.30			-10%	
		Health States & Adverse events: TA514 - Regorafenib	0.30			-11%	
		Health States & Adverse events: CELESTIAL 5L alternative	0.30			-12%	
		Multivariate mixed model for repeat measurement by adjusting treatment arms	0.19			+37%	
Convergence of treatment effects of cabozantinib (OS, PFS, TTD)	No convergence of treatment effects	Convergence applied to survival curves starting median follow-up of 22.9 months	0.22		\$	+8%	
KM data (OS, PFS, TTD) and convergence of treatment effects of cabozantinib	Parametric function adjusted to the whole time-horizon and no convergence	KM data applied up to the median follow-up, and convergence treatment effect applied to the base case parametric functions starting median follow-up of 22.9 months	0.22			+16%	
KM data and exponential function adjusted to OS to both arms.	Log-logistic adjusted to OS to both arms.	KM data up to median follow-up for PFS, OS and TTD, extrapolation based on the submission, except for OS, which was altered to the exponential	0.24			+15%	
KM data and the Gompertz function for OS of cabozantinib and BSC	Log-logistic for OS of cabozantinib and BSC	KM data up to median follow-up for PFS, OS and TTD, extrapolation based on the submission, except for OS that was altered to the Gompertz	0.21			+29%	
Decrease costs of post-progression for cabozantinib by 30%	\$1,957/cycle	\$1,370/cycle	0.27			-17%	
Decrease costs of post-progression for BSC by 30%	\$2,242/cycle	\$1,569/cycle	0.27			+17%	
Correction of possible error in Excel in post-progression costs of	2,242	1,823	0.27			+11%	

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Variable	Base case value (The submission)	Plausible value	Inc. QALYs	Inc. costs	ICER \$/QALY	% ICER change	ICER (ITT)
treatment for BSC							

Abbreviations: 3L = three levels; 5L = five levels; BSC = best supportive care; ICER = incremental cost effectiveness ratio; Inc = incremental; ITT= intention to treat; KM = Kaplan-Meier; QALY = quality adjusted life year; OS = overall survival; PFS = progression free survival; TA = technical analysis; TTD = time to treatment discontinuation;
Source: developed based on the excel model Attachment 13.

- 6.42 The results were most sensitive to restricting the study population to those patients in CELESTIAL who had only received prior sorafenib therapy (i.e. excluding patients treated with multiple systemic therapies prior to cabozantinib); increasing the ICER by 38%. The result for the sorafenib only subgroup is somewhat counterintuitive given that the results from the clinical evidence showed it had HR for both OS and PFS that was consistent with that of the non-Asian subgroup (OS, HR=0.70 compared with 0.71 for the non-Asian region; PFS HR=0.40 compared with 0.45 for the non-Asian region). However, the extrapolation approach resulted in the OS curve for BSC crossing above that of cabozantinib when restricted to the sorafenib only subgroup thereby reducing the QALYs gained relative to the submission’s base case.
- 6.43 The results were next most sensitive to the use of the utility values from the multivariate multiple mixed model that accounted for treatment arms as a variable. Accounting for treatment arms in the model decreased the incremental QALY from 0.27 to 0.19 and increased the ICER by 37%. The results were also sensitive to the exclusion of patients from Asian centres. By including these patients (ITT population), the incremental QALY decreased from 0.27 to 0.20 and increased the ICER by 30%. The model results were also sensitive to the alternative parametric functions applied to the extrapolation of OS. The application of the Gompertz function for OS of cabozantinib and BSC (applied to the Kaplan-Meier data from median follow-up) decreased the incremental QALY from the base case of 0.27 to 0.21 (while slightly increasing incremental costs) and increased the ICER by 29%. The PSCR disagreed with the use of the Gompertz function for OS on the basis that was the parametric function with the highest AIC and BIC metrics.
- 6.44 The ESC considered that the most appropriate base case for the economic evaluation should include the full ITT population, application of KM data up to the point of median follow-up and convergence of treatment effect applied to the base case parametric functions from the point of median follow-up. This re-specified base case resulted in an ICER of \$105,000 - \$200,000 per QALY using the effective price. The PBAC considered that the parameters for the model base case recommended by ESC were appropriate and that use of utilities from the RESORCE trial would be appropriate.

Drug cost/patient/course and year

- 6.45 The effective DPMQ per pack is [REDACTED] per 30-day pack resulting in a cost per course per patient of [REDACTED] for economic model and a cost per year of [REDACTED] for financial estimates. The drug costs in the submission were likely to be underestimated

as they were based on the median duration of exposure rather than the mean. A summary of the drug cost per patient of cabozantinib is provided in Table 12.

- 6.46 The submission proposed flat pricing across the 3 strengths of cabozantinib. The PBAC noted that the recommended cabozantinib daily dose was 60 mg; however, the median average daily dose in the CELESTIAL trial was 35.8 mg, because 62% of patients on cabozantinib required dose reductions. Thus, many patients will potentially not receive the maximum dose, but the cost to the PBS would be the same.

Table 12: Drug cost per patient for proposed and comparator drugs (no discounting applied)

	Proposed drug Trial dose and duration	Proposed drug Model	Proposed drug Financial estimates
Mean dose, mg/day (SD)	36.56 (13.783)	60	41
Mean duration, months (SD)	4.97 (5.47) ^a	6.43	3.8 ^b
Cost/patient/month	█ ^c	█ ^c	█ ^c
Cost/patient	█ course ^d	█ course ^e	█ year

Abbreviations: SD = standard deviation

Source: Table 44 p153 of the CSR; Compiled during the evaluation based on Attachment 13 (economic model) and 14 (financial estimates)

Note: ^a The figure was mean duration of treatment while the mean duration of exposure was 5.87 (5.895) months.

^b Median duration of 3.8 months was rounded up to 4 months per the submission.

^c Flat prices across three strengths, 30 tablets per pack.

^d the mean duration of treatment of 4.97 months (rounded up to 5 months).

^e Over the entire time horizon of 5 years.

Estimated PBS usage & financial implications

- 6.47 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the expected financial impact associated with the listing of cabozantinib based on the published price. Data on the current use of sorafenib (a market share approach) were presented as a means of externally validating the estimate of patients with HCC.
- 6.48 The financial estimates for the use of cabozantinib per the submission (published price) are presented in Table 13.

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Table 13: Estimated use and financial implications (published price)

	2019	2020	2021	2022	2023	2024
Estimated extent of use						
Number of patients treated						
Number of scripts dispensed ^a						
Estimated financial implications of cabozantinib						
Cost to PBS/RPBS						
Copayments						
Cost to PBS/RPBS less copayments						
Estimated financial implications for BSC						
Cost to PBS/RPBS less copayments	0	0	0	0	0	0
Net financial implications						
Net cost to PBS/RPBS						
Net cost to MBS						
Net cost to PBS/RPBS/MBS/						

Abbreviations: MBS= Medicare Benefits Schedule; PBS= Pharmaceutical Benefit Scheme; RPBS= Repatriation Schedule of Pharmaceutical Benefits.

Source: Table 4-8, p. 236; Table 4-8, p. 236; Table 4-9 of the submission; developed during the evaluation

Note: ^a Assuming 4 per year as estimated by the submission.

The redacted table shows that the estimated number of patients treated at year 6 would be less than 10,000, and the net cost to PBS/RPBS would be \$30 - \$60 million.

6.49 The financial estimates for the use of cabozantinib using the effective price are presented in Table 14.

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Table 14: Estimated use and financial implications (effective price)

	2019	2020	2021	2022	2023	2024
Estimated extent of use						
Number of patients treated						
Number of scripts dispensed ^a						
Estimated financial implications of cabozantinib						
Cost to PBS/RPBS						
Copayments						
Cost to PBS/RPBS less copayments						
Estimated financial implications for BSC						
Cost to PBS/RPBS less copayments	0	0	0	0	0	0
Net financial implications						
Net cost to PBS/RPBS						
Net cost to MBS						
Net cost to PBS/RPBS/MBS/						

Abbreviations: MBS= Medicare Benefits Schedule; PBS= Pharmaceutical Benefit Scheme; RPBS= Repatriation Schedule of Pharmaceutical Benefits.

Source: developed during the evaluation

Note: ^a Assuming 4 per year as estimated by the submission.

The redacted table shows that at year 6 the total number of patients treated would be less than 10,000 and the net cost to PBS/RPBS from \$10 - \$20 million.

6.50 The submission overestimated the number of HCC patients treated with sorafenib, and thus the number eligible to receive cabozantinib. This arose because the submission based its assumption regarding the proportion of sorafenib patients that would meet the PBS criteria (Child-Pugh A) on Doyle et al (2016) that only recruited patients who had already received sorafenib, and thus were likely to have met the PBS criteria. Thus, the data from that study did not reflect the incidence of patients meeting those criteria among the overall HCC population. A recent review of general HCC patients in Australia (Hong et al (2018)), indicated that 56% had Child-Pugh A. While it was unknown what combination of patients would meet both BCLC B or C and Child-Pugh A, it was reasonable to expect that the proportion of patients that could meet both criteria would not exceed 56% (optimistically assuming that all Child-Pugh A had BCLC B or C). The submission assumed that 75% of HCC patients met the PBS eligibility criteria for sorafenib. Based on the Hong et al (2018) data, this would appear to be an overestimate. The comparison of the epidemiological approach with current use of sorafenib on the PBS supports the assertion that cabozantinib use was overestimated in the submission. Using the number of sorafenib treated patients from the market share approach would reduce the number of patients that would be eligible for cabozantinib to around half that estimated by the submission. This would reduce the net financial impact implications to the PBS/RPBS by 50% each year.

- 6.51 The submission used median duration of treatment (3.8 months) from CELESTIAL to estimate the number of packs required by patient per year (rounded up to 4 months). The use of median duration of treatment (instead of mean) was inappropriate. Based on the economic model, the mean duration of treatment was 6.43 months (rounded to 7 months). As such, the submission underestimated the number of packs required per year by 3 months. Adjusting for this underestimate would increase the net financial impact to the PBS/RPBS by 75% each year.
- 6.52 The sponsor recalculated the financial estimates in the pre-PBAC response, using the alternative inputs suggested in the ESC advice, decreasing the eligible population from 75% to 56% and increasing the duration of treatment from 3.8 (rounded up to 4) months to 6.43 (rounded up to 7) months. This increased the financial net cost to the PBS/RPBS from \$20 - \$30 million in year 6, based on the proposed effective price. The PBAC considered that both the model and financial estimates should have used a mean duration consistent with the trial duration.

Financial Management – Risk Sharing Arrangements

- 6.53 No risk-sharing arrangement (RSA) was proposed in the submission. The submission stated that the sponsor intends to enter into a special price arrangement (SPA) for cabozantinib for patients with HCC who progress on previous treatment with a prior-TKI (sorafenib).

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend cabozantinib for the treatment of BCLC B or C advanced HCC who have been previously treated with sorafenib. The PBAC considered the clinical benefits of cabozantinib were modest with considerable toxicity. The PBAC considered at the proposed price the ICER was unacceptably high for the minor benefit in this setting and substantial cost reductions would be required to bring the ICER into an acceptable range. The PBAC was also concerned that the financial impact of listing cabozantinib is uncertain.
- 7.2 The PBAC considered that use beyond progression would not be appropriate and this should be included in the restrictions as proposed. The PBAC considered the restriction wording should also specify that patients treated with cabozantinib are required to have progressed on a first line TKI. The PBAC agreed with the ESC that despite the lack of evidence post lenvatinib, it would be appropriate to allow clinicians to determine the most appropriate first line TKI for patients prior to cabozantinib.
- 7.3 The PBAC noted that there are currently no PBS-listed second-line options for HCC. The PBAC noted that there is a clinical need for second-line treatment in this patient group, although the listing of lenvatinib assists somewhat in addressing the need where patients are intolerant to sorafenib. The PBAC considered that, against a

background of poor OS in advanced HCC, the results for cabozantinib were both statistically significant and clinically meaningful. However, the PBAC considered that cabozantinib would not fully meet the substantial clinical need, as it has significant toxicity and only a minor benefit.

- 7.4 The submission nominated BSC as the main comparator for the primary clinical claim of superiority. The submission included a secondary indirect comparison to regorafenib. The PBAC considered that given no other therapy is listed for second-line treatment, the submission appropriately uses BSC as the main comparator, with regorafenib as a secondary “near-market” comparator.
- 7.5 The PBAC noted that the evidence for cabozantinib compared to BSC was informed by the CELESTIAL trial (n=707), which is a Phase 3, randomised, double blind, placebo-controlled study of cabozantinib in patients with HCC who have received prior sorafenib.
- 7.6 The PBAC noted that the CELESTIAL trial showed a statistically significant improvement in PFS for cabozantinib; however, patients treated with cabozantinib were more likely to die without progressing compared to BSC, although the difference was not statistically significant. The PBAC noted that the CELESTIAL trial showed a statistically significant improvement in the estimated OS for cabozantinib; however, the Kaplan-Meier curves for OS curves converged at around 34 months and cross soon thereafter. At this time point the number of patients at risk was very low, complicating the interpretation of any OS difference after that point.
- 7.7 The PBAC considered that the claim of superior comparative effectiveness of cabozantinib compared with BSC was reasonable; however, the clinical benefits of cabozantinib were minor.
- 7.8 The PBAC considered that the claim of inferior comparative safety of cabozantinib compared with BSC was reasonable. The PBAC noted that the adverse event profile of cabozantinib is not benign, leading to discontinuations, interruptions, and reductions, but considered the description of “manageable” is still reasonable for the majority of patients, aided by the flexibility in dose. The PBAC noted that safety profile of cabozantinib is not fully characterised in HCC.
- 7.9 The PBAC noted that the evidence for cabozantinib compared to regorafenib was informed by the RESORCE trial (n=573), with BSC as the common reference, in an ITC. RESORCE is a Phase 3, randomised, double blind, placebo-controlled study of regorafenib in patients with HCC who have received prior sorafenib.
- 7.10 The PBAC noted that the HRs reported for the ITC in the submission were not consistent with the ORs provided in the ITC workbook. The ITC results indicated that there was no difference in clinical effect between cabozantinib and regorafenib in terms of OS; however, there was some difference in PFS in favour of regorafenib. The PBAC considered that the claim of non-inferior OS of cabozantinib compared with regorafenib, using BSC as the common reference, was reasonable. The PBAC

considered that the claim of non-inferior PFS and ORR compared with regorafenib was not supported by the evidence.

- 7.11 The PBAC noted that the PSCR provided a report for a MAIC of cabozantinib compared with regorafenib to address the transitivity issues identified between the CELESTIAL and RESORCE trials. The MAIC included comparative efficacy and safety considering the pure second-line patients from CELESTIAL (excluding patients who received cabozantinib as third line treatment in CELESTIAL), relative to those in RESORCE. Results were consistent with those in the submission in terms of OS (no statistical differences) but not for PFS where statistical differences were found favouring cabozantinib. However, the additional data have not been evaluated as they were provided with the PSCR.
- 7.12 The PBAC considered that the claim of non-inferior comparative safety of cabozantinib compared with regorafenib in the ITC was not adequately supported by the data. The PBAC considered that the safety data were inconclusive, noting that apparent differences in safety events may be because the CELESTIAL trial recruited both second- and third-line patients while the RESORCE trial recruited second-line patients only. The PBAC noted that the rate of diarrhoea is significantly higher for cabozantinib compared with regorafenib in the MAIC, where second-line line cabozantinib patients are compared with second-line regorafenib patients. Overall, the PBAC considered it likely that in clinical practice, the safety profile of cabozantinib and regorafenib would be comparable.
- 7.13 The PBAC noted that the evaluation and ESC had identified a number of issues regarding the CUA versus BSC, including:
- exclusion of Asian sites, which reduced the sample size;
 - use of a 5 year time horizon, despite only 18% of cabozantinib patients alive at 24 months;
 - lack of convergence of Kaplan-Meier curves in the model, despite the trial-based curves converging at 34 months;
 - extrapolation methods were inadequately justified and extrapolation was applied to the whole time horizon rather than including Kaplan-Meier data up to the point of median follow-up; and
 - HRQoL data obtained directly from CELESTIAL was not applied in the economic model, application of QoL data via the regression models chosen did not capture the inferior QoL experienced for patients treated with cabozantinib.
- 7.14 The PBAC noted that the model was sensitive to the exclusion of the Asian sites and considered that exclusion of Asian sites was not justified. The PBAC noted that the model was sensitive to use of the sub-population in CELESTIAL who received sorafenib as their only prior treatment. The PBAC noted that use of this population increased the ICER despite superior OS and PFS results in this group of patients, suggesting that the extrapolation methods were problematic. The PBAC considered that the utilities should be applied in the model such that the inferior QoL for cabozantinib in

CELESTIAL is fully captured.

- 7.15 The PBAC noted that the ESC had proposed a re-specified base case using (i) the full ITT population; (ii) application of Kaplan-Meier data up to the point of median follow-up; and (iii) convergence of treatment effect applied to the base case parametric functions from the point of median follow-up. The PBAC considered that this was more appropriate than the base case presented in the submission, and noted that this analysis increased the ICER from \$10,000 - \$200,000/QALY gained using the effective price proposed in the submission. The PBAC considered that, even without adjusting for the model issues, the ICER was unacceptably high at the proposed price for the level of potential benefit in this setting. The PBAC considered that the revised base case ICER was very high and the cost for cabozantinib would need to be reduced substantially to bring the ICER into an acceptable range. The PBAC considered that for the minor clinical benefit of cabozantinib and significant toxicity, an ICER of \$40,000 or less would be appropriate.
- 7.16 The submission proposed that the same price should apply across the 3 strengths of cabozantinib. The PBAC noted that the recommended cabozantinib daily dose was 60 mg; however, the median average daily dose in the CELESTIAL trial was 35.8 mg due to dose reductions, with 38%, 29%, 33% on 60 mg, 40 mg, 20 mg doses respectively. Thus, many patients will potentially not receive the maximum dose, but the cost for treatment would be the same. There was insufficient information on the dose response relationship to indicate the effectiveness impact if fewer or more patients required lower doses to accommodate toxicity than was seen in the trial. The PBAC considered that this pricing structure may therefore not be reasonable in this indication and suggested that reductions in the cost of the lower doses may enable a reduction in the overall cost of cabozantinib and therefore assist in bringing the ICER into an acceptable range.
- 7.17 The PBAC considered that the submission overestimated the proportion of advanced HCC patients and underestimated the mean duration of time on treatment for cabozantinib. The sponsor assumed that 75% of HCC patients would be eligible for sorafenib (Child-Pugh A), but recent Australian data suggests this figure is 56%. The PBAC noted that the sponsor recalculated the financial estimates in the pre-PBAC response, using the alternative inputs suggested in the ESC advice, by decreasing the eligible population from 75% to 56% and increasing the duration of treatment from 3.8 months to 6.43 months. This resulted in an overall increase in the net cost to the PBS/RPBS, based on the effective price, from \$20 - \$30 million in year 6.
- 7.18 The PBAC considered that the overall cost was very high at the proposed price, and highly uncertain. The PBAC considered that a RSA would be required to manage this uncertainty.
- 7.19 The PBAC considered that any future submission would need to be a major submission. The PBAC considered that a substantial price reduction and reduction in the ICER would be required to achieve cost-effectiveness of cabozantinib in advanced

HCC, and the issues associated with the proposed economic model would need to be addressed.

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

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised 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.

9 Sponsor's Comment

Ipsen is disappointed with this outcome, as there presently is a clear unmet clinical need for patients with HCC in this setting. We are committed to continue working with clinicians, the Department of Health and the PBAC to determine whether there is a way forward for future submissions.