

7.08 CABOZANTINIB

**Tablet 20 mg,
Tablet 40 mg,
Tablet 60 mg,
Cabometyx[®],
Ipsen Pty Ltd.**

1 Purpose

- 1.1 The early re-entry resubmission requested a General Schedule Authority Required (STREAMLINED) listing for cabozantinib as monotherapy for the treatment of adult and paediatric patients aged 12 years and older with locally advanced or metastatic differentiated thyroid carcinoma (DTC) who are radioactive iodine (RAI) refractory or ineligible, who have progressed following treatment with a tyrosine kinase inhibitor (TKI) or have developed intolerance to prior vascular endothelial growth factor (VEGF) targeted therapy.
- 1.2 The resubmission was based on the PBAC decision to not recommend cabozantinib for this indication from November 2023. This resubmission addressed the issues raised by PBAC; see Table 1 below.

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Table 1: Issues raised by PBAC from the November 2023 submission for cabozantinib

Matter of concern	Response	Addressed?
Revisions to the restriction including: <ul style="list-style-type: none"> the addition of the clinical criterion to the initial supply restriction stating that patients must have thyroid stimulating hormone adequately repressed; and amending the initial supply restriction to align with the COSMIC-311 trial in terms of WHO/ECOG score (i.e. changing the requirement of having a WHO performance status from not greater than 2 to not greater than 1. 	The early re-entry resubmission: <ul style="list-style-type: none"> added this clinical criterion; and did not make this change. 	Yes No
Revisions to the economic model including: <ul style="list-style-type: none"> basing the economic model on the subgroup of patients who had received prior lenvatinib only; apply the trial-based utility for the pre-progression health state (0.692). To which the relative utility decrement from Fordham (2015) of -0.278 should be applied to determine the post-progression utility (0.414); remove all treatment costs from the post-progression health state; and reduce the price of cabozantinib to result in an ICER of less than \$95,000 to < \$115,000 per QALY. 	The early re-entry resubmission: <ul style="list-style-type: none"> presented base case results based on the subgroup of patients who had received prior lenvatinib only. The resubmission also presented a sensitivity analysis using the full ITT population; applied utility values as requested; all treatment costs were removed; however, end-of-life costs were added price of cabozantinib was reduced by 12% to result in an ICER of \$55,000 to < \$75,000 per QALY 	Yes Yes Partially No. If end-of-life costs are removed, the ICER increased to \$155,000 to < \$255,000 per QALY.
Base the utilisation estimates on the utilisation data for lenvatinib.	The early re-submission based the utilisation estimates on the lenvatinib data. A number of other changes were also made in line with the November 2023 PBAC minutes.	Yes

Source: compiled from the November 2023 cabozantinib minutes and the March 2024 early re-entry resubmission
 ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; QALY = quality adjusted life year; WHO = World Health Organisation

2 Background

2.1 Cabozantinib was registered on the ARTG on 9 December 2022 for the following indication:

- The treatment of adult and paediatric patients aged 12 years and older with locally advanced or metastatic differentiated thyroid carcinoma (DTC) that has progressed during or after prior VEGF-targeted therapy and who are radioactive iodine (RAI) refractory or ineligible.

2.2 The PICO from the previous submission is presented below.

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Table 2: Key components of the clinical issues

Component	Description
Population	Patients with DTC refractory or not eligible to RAI who have progressed during or after prior VEGF-targeted therapy and have a WHO performance status of 2 or less ^a
Intervention	Cabozantinib, 60 mg orally once daily (QD) until disease progression or unacceptable toxicity.
Comparator	Best supportive care (placebo)
Outcomes	Progression-free survival (PFS) Objective response rate (ORR) Safety
Clinical claim	In patients with DTC refractory or not eligible to RAI who have progressed after prior systemic therapy ^a , and a WHO performance status of 2 or less, cabozantinib provides: <ul style="list-style-type: none"> Significantly superior PFS and ORR compared to standard of care, and An inferior but manageable safety profile

Source: Table 1.1, p16 of the submission.

DTC = differentiated thyroid carcinoma; ORR = objective response rate; PFS = progression-free survival; RAI = radioactive iodine; VEGF = vascular endothelial growth factor; WHO = World Health Organisation.

^a This was inaccurate. The proposed restriction was for patients that have progressed following treatment with a tyrosine kinase inhibitor or have developed intolerance to prior VEGF-targeted therapy

For more detail on PBAC's view, see Section 5 PBAC outcome.

3 Requested listing

3.1 The resubmission presented a revised proposed restriction based on the suggestions in the November 2023 PBAC minutes.

3.2 Secretariat additions are in italics and deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOZANTINIB					
Cabozantinib 20 mg tablet, 30 40 mg tablet, 30 60 mg tablet, 30	Published: \$9,962.13 Effective: \$ 1	1	30	2	Cabometyx, Ipsen Pty Ltd

Category / Program: Section 85 (General Schedule)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Streamlined
Severity: Locally advanced or metastatic
Condition: Differentiated thyroid carcinoma
PBS Indication: Locally advanced or metastatic differentiated thyroid carcinoma
Treatment phase: Initial treatment
Clinical criteria:
The condition must be refractory to radioactive iodine; or
Patient must be deemed ineligible for treatment with radioactive iodine,
AND
Clinical criteria:
Patient must have progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) whilst on treatment with a vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor (TKI) for this indication;
OR

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Patient must have developed intolerance of a severity necessitating permanent treatment withdrawal, in the absence of disease progression, to prior VEGF-targeted TKI therapy
AND
Clinical criteria:
Patient must have a WHO performance status of not greater <i>higher</i> than 2,
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria:
Patient must have thyroid stimulating hormone adequately repressed <i>suppressed</i>
Population criteria:
Patient must be aged 12 years or older
Prescribing instructions:
Radioactive iodine refractory is defined as:
<ul style="list-style-type: none"> • a lesion without iodine uptake on a radioactive iodine (RAI) scan; or • having received a cumulative RAI dose of greater than or equal to 600 mCi; or • progression within 12 months of a single RAI treatment; or • progression after two RAI treatments administered within 12 months of each other
Administrative Advice: No increase in the maximum quantity or number of units may be authorised
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Note:
Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all targeted 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.
Note:
Vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor's (TKI) include: lenvatinib

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CABOZANTINIB					
Cabozantinib 20 mg tablet, 30 40 mg tablet, 30 60 mg tablet, 30	Published: \$9,962.13 Effective: \$█	1	30	5	Cabometryx, Ipsen Pty Ltd

Category / Program: Section 85 (General Schedule)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Streamlined
Severity: Locally advanced or metastatic
Condition: Differentiated thyroid carcinoma (DTC)
PBS Indication: Advanced or metastatic differentiated thyroid carcinoma
Treatment phase: Continuing treatment
Clinical criteria:

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The condition must be refractory to radioactive iodine; or
Patient must be deemed ineligible for treatment with radioactive iodine,
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
Treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria:
Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST).
Administrative Advice: No increase in the maximum quantity or number of units may be authorised
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Note:
Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all targeted 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.
Note:
Vascular endothelial growth factor (VEGF) targeted tyrosine kinase inhibitors (TKI) include: lenvatinib

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Category / Program: Section 85 (General Schedule)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Streamlined
Severity: Locally advanced or metastatic
Condition: Differentiated thyroid carcinoma (DTC)
PBS Indication: Locally advanced or metastatic differentiated thyroid carcinoma
Treatment phase: Grandfather supply
Clinical criteria:
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date];
AND
Clinical criteria:
The condition must be refractory to radioactive iodine; or
Patient must be deemed ineligible for treatment with radioactive iodine,
AND
Clinical criteria:

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Patient must have had progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) whilst on treatment with a vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor (TKI) prior to receiving this drug for this indication;
OR
Patient must have developed intolerance of a severity necessitating permanent treatment withdrawal, in the absence of disease progression, to prior VEGF-targeted TKI therapy prior to receiving this drug for this indication
AND
Clinical criteria:
Patient must have a WHO performance status of not greater than 2 prior to receiving this drug for this indication
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria:
Patient must have thyroid stimulating hormone adequately repressed <i>suppressed</i>
Population criteria:
Patient must be aged 12 years or older.
Prescribing instructions:
Radioactive iodine refractory is defined as:
<ul style="list-style-type: none"> • a lesion without iodine uptake on a radioactive iodine (RAI) scan; or • having received a cumulative RAI dose of greater than or equal to 600 mCi; or • progression within 12 months of a single RAI treatment; or • progression after two RAI treatments administered within 12 months of each other
Administrative Advice: No increase in the maximum quantity or number of units may be authorised
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Note:
Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all targeted 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.
Note:
Vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor's (TKI) include: lenvatinib

- 3.3 The restriction proposed in the resubmission included a clinical criterion in the initial supply and grandfather restrictions stating that patients must have thyroid stimulating hormone adequately repressed, which is consistent with the lenvatinib listing.
- 3.4 The proposed restriction again required a World Health Organization (WHO) performance status of no greater than 2, whereas the COSMIC-311 trial required patients have and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- 3.5 The resubmission stated that the estimated number of grandfather patients receiving cabozantinib through a patient access program had increased from 15 in November 2023 to 20 in this submission.

For more detail on PBAC's view, see Section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item. The PBAC recalled that the sponsor hearing from November 2022 was informative in describing the clinical need for additional therapies in this setting.

Consumer comments

- 4.2 Although no consumer comments were received for this item, the PBAC recalled that in November 2022 input from health care professionals (2) and organisations (1) was received via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cabozantinib including the prolonged progression free survival in patients with differentiated thyroid cancer that has progressed on first-line treatment. The advice received from the Australian Thyroid Foundation also noted that listing cabozantinib on the PBS would improve equity.

Clinical evidence

- 4.3 The November 2023 submission was based on one randomised controlled trial, COSMIC-311, that compared cabozantinib to placebo. The PBAC noted that patients were stratified by previous lenvatinib treatment (yes/no) and age (≤ 65 years versus > 65 years). Results for the subgroup of patients who had received prior treatment with lenvatinib only were presented as it aligned with the proposed place in therapy.
- 4.4 Cabozantinib was associated with a modest improvement in overall response rate (ORR) in the full intention to treat (ITT) population (risk difference = 11%; 95% CI: 6.4%, 15.9%). Cabozantinib also demonstrated a statistically significant improvement in progression free survival (PFS) in both the full ITT population (HR = 0.22; 95% CI: 0.15, 0.32) and the subgroup who had received prior treatment with lenvatinib only (HR = 0.28; 95% CI: 0.16, 0.48).
- 4.5 The results for overall survival were not statistically significant in either the full ITT population (HR = 0.76; 95% CI: 0.45, 1.31) or the subgroup who had received prior treatment with lenvatinib only (HR = 1.06; 95% CI: 0.45, 2.47). The overall survival results were confounded by 45% of patients in the placebo arm crossing over to receive treatment with open label cabozantinib following disease progression. Therefore, the November 2023 submission applied the Rank-Preserving Structural Failure Time (RPSFT) method to adjust for the crossover; however, this did not result in a statistical difference in the results (full ITT population: HR = 0.65; 95% CI: 0.28, 1.53; prior lenvatinib only subgroup: HR = 0.98; 95% CI: 0.24, 3.91). Additionally, a high proportion of observations were censored in both the cabozantinib (78%) and placebo (76%) arms which was driven by the relatively short median follow up (10.1 months).
- 4.6 In terms of safety, patients in the cabozantinib arm of COSMIC-311 reported a higher incidence of Grade 3/4 adverse events (62% versus 28% for patients in the placebo

arm) and had a higher incidence of hypertension, diarrhoea, palmar-plantar erythrodysesthesia syndrome and fatigue.

Clinical claim

- 4.7 In November 2023, the PBAC considered that the submission's claim that cabozantinib was superior compared to placebo in terms of ORR and PFS was supported. However, the PBAC considered that the superiority of cabozantinib in terms of OS was uncertain due to patients randomised to placebo receiving cabozantinib, the relatively short follow up and the high number of observations that were censored (paragraph 7.10, cabozantinib minutes, November 2023).
- 4.8 In November 2023, the PBAC considered that the claim that cabozantinib was inferior in terms of safety compared to placebo was reasonable (paragraph 7.11, cabozantinib minutes, November 2023).
- 4.9 The PBAC's consideration of the comparative clinical effectiveness and safety remain unchanged from November 2023.

Economic analysis

- 4.10 In November 2023, the PBAC considered that the economic model was uncertain and that the base case ICER presented in the submission (\$55,000 to < \$75,000 per QALY) was underestimated (paragraph 7.1, cabozantinib minutes, November 2023). The PBAC suggested that a more appropriate base case would:
- continue to be based on the subgroup of patients who had received prior lenvatinib only;
 - apply the trial-based utility to the pre-progression health state (0.692). The relative utility decrement from Fordham (2015) of -0.278 should then be applied to determine the post-progression utility (0.414); and
 - remove all treatment costs from the post-progression health state.
- 4.11 The PBAC noted that the ICER for the above scenario was \$155,000 to < \$255,000 per QALY and considered that a price reduction would be required for cabozantinib to be considered cost effective. Noting the rare nature of RAI refractory or ineligible DTC, the poor prognosis following progression, the potentially conservative model assumptions with regards to the use of the subgroup data and removal of all post progression costs and the small budget impact, an ICER of less than \$95,000 to < \$115,000 per QALY would be cost effective in this setting (paragraph 7.15, cabozantinib minutes, November 2023).
- 4.12 As noted in Table 1, the resubmission accepted the changes to the utility values, partially accepted the removal of all post progression treatment costs (all treatment costs were removed, but end-of-life costs were incorporated), presented results using subgroup who had previously received lenvatinib only and proposed a 12% reduction

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to the effective DPMQ of cabozantinib. These changes resulted in an ICER of \$55,000 to < \$75,000 per QALY; see Table 3.

Table 3: Results of the economic model and the changes requested by PBAC in November 2023

	Incremental costs (\$)	Incremental QALYs	ICER
November 2023 submission base case		0.18	1
March 2024 revisions			
Revision of utility values		0.14	2
+ Removal of post-progression treatment costs		0.14	3
+ Addition of end-of-life costs of \$4,549.91 per cycle		0.14	2
+ Revised DPMQ of \$3,025.73		0.14	1
Sensitivity analyses			
March 2024 revisions + full ITT population		0.30	4
March 2024 revisions + removal of end-of-life costs		0.14	3
March 2024 revisions + full ITT population + removal of end-of-life costs		0.30	5

Source: Table 3-3, p24 of the early re-entry submission; and Excel workbook – CBZIND – 1.XLS

DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

- ¹ \$55,000 to < \$75,000
- ² \$75,000 to < \$95,000
- ³ \$155,000 to < \$255,000
- ⁴ \$15,000 to < \$25,000
- ⁵ \$135,000 to < \$155,000

- 4.13 The resubmission, noting that the November 2023 minutes stated that ‘the use of a subgroup increased the extent of uncertainty with the results [of the economic model] given the relatively small number of patients informing the analysis’ (paragraph 7.12, cabozantinib minutes, November 2023) and ‘the potentially conservative model assumptions with regards to the use of the subgroup data’ (paragraph 7.15, cabozantinib minutes, November 2023), considered that the full ITT population data was more representative of the true impact of PFS in the target population than using the subgroup of patients who had received prior lenvatinib only. Therefore, the resubmission presented a sensitivity analysis in which the full ITT population was used.
- 4.14 The resubmission stated that it did not consider that the removal of all post progression treatment costs was reasonable and that it was appropriate to incorporate some relevant costs post progression. The resubmission noted that during the November 2023 Sponsor hearing, the clinician commented ‘that once patients cease treatment with lenvatinib they decline very quickly’ (paragraph 6.1, cabozantinib minutes, November 2023). Therefore, the resubmission incorporated the end-of-life health care costs into the economic analysis. The mean cost of palliative care and health care for Australian cancer patients in their final year of life of \$55,037 was sourced from Kenny (2023). A cost of \$4,549 per cycle was applied to all patients in the post progression health care state.

Estimated PBS usage and financial implications

4.15 In November 2023, the PBAC noted that the utilisation and financial estimates were overly complex and advised that a modified market share approach based on the utilisation data for lenvatinib would be more reliable. The PBAC advised that if this approach was adopted, then an average of incident lenvatinib patients from 2020 to 2023 could be used as a base. The PBAC considered that approximately 60% of patients who received lenvatinib would be eligible to receive second line cabozantinib (based on the clinician hearing) (paragraph 7.16, cabozantinib minutes, November 2023).

4.16 The resubmission has provided revised financial estimates which incorporated the PBAC’s suggested changes and updated other inputs based on comments in the November 2023 minutes. Table 4 presents a comparison of the utilisation inputs.

Table 4: Comparison of key utilisation inputs from November 2023 to March 2024

Parameter	November 2023 input	November 2023 PBAC comment	March 2024 input
Incidence of thyroid cancer	Incidence of thyroid cancer 13.9/100,000 based on AIHW cancer data, assumed constant throughout Years 1-6.	Likely underestimated as the incidence rate of thyroid cancer has been increasing at a rate of 2.7% ¹ per year.	Number of incident patients has been increased by 2.7% per year.
Incident patients	<ul style="list-style-type: none"> 94% of thyroid cancer patients had DTC; 27.5% of DTC patients had advanced/metastatic disease; 33.3% of patients with advanced/metastatic disease were refractory to RAI; 37.5% of patients with RAI-R DTC were treated with 1L TKI; 53.1% of 1L-treated patients with progressed disease 100% patient share in 2L (assumption of 100% uptake) 	Uncertain. The ESC noted that the DUSC Secretariat provided a count of patients who had received lenvatinib in the first line setting which indicated that incident patient numbers may have been overestimated.	Updated the approach. Incident patients now derived from the count of patients who had received lenvatinib in first line setting, as per Table 24, cabozantinib minutes, November 2023. The eligibility of this patient population is 60% to reflect those likely to transition onto cabozantinib as specified by the PBAC (paragraph 7.16, cabozantinib minutes, November 2023).
Prevalent patients	█████ ¹ in Year 1, none in other years.	Uncertain. Based on the estimated number of incident patients in Year 1.	█████ ¹ in Year 1. As the estimated number of grandfather patients was increased from █████ ¹ to █████ ¹ (see below), the number of prevalent patients was reduced accordingly to avoid double counting.

¹ Average annual growth rate of thyroid cancer incidence 2020-2022, calculated during the evaluation based on data from Table S1a.1: Cancer incidence counts, age-specific rates, age-standardised rates (2001 Australian Standard, WHO and Segi populations), by sex, age group, actual data from 1982 to 2018 and projections to 2022, Data tables: CDIA 2022: Book 1a – Cancer incidence (age-standardised rates and 5-year age groups), Cancer data in Australia, web report, last updated 4 October 2022 [available: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data>; accessed 2 August 2023].

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Parameter	November 2023 input	November 2023 PBAC comment	March 2024 input
Grandfather patients	█ ¹ in Year 1, none in other years. Currently █ ¹ patients were enrolled in the Ipsen Patient Access Program and on active treatment; assumed 100% meeting the proposed PBS restrictions and 100% electing continuing cabozantinib treatment.	It is unclear how many patients will be on the access program at the time of a listing.	Has increased from █ ¹ to █ ¹ patients to reflect estimate at time of listing from compassionate access program.
Treatment duration	Incident patients: eight months per course per patient, based on the extrapolated average time (0.67 year) on treatment from the economic model.	-	Unchanged
	Prevalent patients: 12 months	Over-estimated, should be the same, or possibly less than, for incident patients (i.e., eight months).	Amended to 8 months to align with incident patients.
	Grandfathered patients: 4 months	-	Unchanged
MBS 55145	\$496 (\$513.85) Pharmacological stress ECG	MBS item 55145 cannot be co-claimed with MBS item 11729	Kept MBS item 55145, removed MBS item 11729
MBS 11729	\$160.90 (\$166.60) Multi-channel ECG	Inappropriate if MBS item 55145 was claimed already.	Removed MBS item 11729 as above
DPMQ of cabozantinib	\$█	-	\$█

Source: Table 4-1, pp27-28 of the March 2024 early re-entry resubmission

1L = first-line; 2L = second-line; AIHW = Australian Institute of Health and Welfare; DTC = differentiated thyroid cancer; ECG = electrocardiogram; MBS = Medicare Benefits Schedule; RAI = radioactive iodine; RAI-R = radioactive iodine-refractory; TKI = tyrosine kinase inhibitor.

The redacted values correspond to the following ranges:

¹ < 500

4.17 Table 5 presents the revised utilisation and financial estimates and provides a comparison with the November 2023 results.

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Table 5: Estimated utilisation and financial impact estimates

	Year 1 2024	Year 2 2025	Year 3 2026	Year 4 2027	Year 5 2028	Year 6 2029
Estimated extent of use						
Number of patients treated	1 ^a	1	1	1	1	1
Number of scripts dispensed ^b	2	1	1	1	1	1
Estimated financial implications of cabozantinib						
Cost to PBS/RPBS less co-pay ^c	3	3	3	3	3	3
Estimated financial implications for other medicines						
Cost to PBS/RPBS less co-pay	3	3	3	3	3	3
Net financial implications						
Net cost to PBS/RPBS	3	3	3	3	3	3
Net cost to MBS	3	3	3	3	3	3
Net cost to PBS/RPBS/MBS	3	3	3	3	3	3
November 2023 submission						
Estimated extent of use						
Number of patients treated	1 ^a	1	1	1	1	1
Number of scripts dispensed ^b	2	1	1	1	1	1
Estimated financial implications of cabozantinib						
Cost to PBS/RPBS less co-payments	3	3	3	3	3	3
Estimated financial implications for other medicines						
Cost to PBS/RPBS less co-payments	3	3	3	3	3	3
Net financial implications						
Net cost to PBS/RPBS	3	3	3	3	3	3
Net cost to MBS	3	3	3	3	3	3
Net cost to PBS/RPBS/MBS	3	3	3	3	3	3

Source: Tables 4-2, 4-4 and 4-6, pp29, 31 and 33 of the March 2024 early re-entry resubmission, Cabometyx DTC Section 4 Resubmission March 2024 FINAL excel workbook and Table 23, p41 of the cabozantinib minutes, November 2023

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a ■ patients = ■ incident patients + ■ prevalent patients + ■ grandfathered patients

^b Assuming 8 months treatment per course per patient, based on the extrapolated average time (0.67 year) on treatment from the economic model.

^c PBS co-payment = \$16.21; RPBS copayment = \$5.84

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

4.18 The revised estimated net cost to the PBS/RPBS was \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6 and totalling an estimated \$0 to < \$10 million over the first 6 years of listing. The November 2023 submission estimated a total cost of \$0 to < \$10 million over the first 6 years of listing.

For more detail on PBAC's view, see Section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended cabozantinib, on the basis that it should be available as a General Schedule Authority Required (STREAMLINED) listing, for the treatment of locally advanced or metastatic differentiated thyroid carcinoma (DTC) in patients who are radioactive iodine (RAI) refractory or ineligible, who have progressed following treatment with a tyrosine kinase inhibitor (TKI) or have developed intolerance to prior vascular endothelial growth factor (VEGF) targeted therapy. The PBAC considered that there was a clinical need for additional treatments in this setting. The PBAC noted that the resubmission made the requested changes to the economic model but considered that the approach for including end-of-life costs was inappropriate. However, the PBAC considered that the addition of some post-progression costs would be appropriate, and that cabozantinib would likely be cost-effective at the price proposed in the submission. The PBAC noted that the estimated financial impact was small.
- 5.2 The PBAC recalled that it had previously considered that cabozantinib was superior compared to placebo in terms of ORR and PFS; however, superiority in terms of OS was uncertain. This was based on the results of the COSMIC-311 trial, in which cabozantinib was associated with:
- a modest improvement in overall response rate (ORR);
 - statistically significant improvements in progression free survival (PFS) in both the full intention to treat (ITT) population (HR = 0.22; 95% CI: 0.15, 0.32) and the subgroup who had received prior treatment with lenvatinib only (HR = 0.28; 95% CI: 0.16, 0.48); and
 - overall survival (OS) results which were not statistically significant in either population. It was noted that the OS results were confounded by 45% of patients in the placebo arm crossing over to receive treatment with cabozantinib following disease progression.
- 5.3 In terms of safety, the PBAC recalled that it had previously considered that cabozantinib was inferior to placebo.
- 5.4 The PBAC recalled that it had specified the following revisions to the economic model would be required to achieve an acceptable incremental cost-effectiveness ratio (ICER):
- The application of the trial-based utility to the pre-progression health state (0.692). The relative utility decrement from Fordham (2015) of -0.278 should then be applied to determine the post-progression utility (0.414).
 - Removal of all treatment costs from the post-progression health state.
 - A price reduction so that the resulting ICER was less than \$95,000 to < \$115,000 per quality adjusted life year (QALY) gained.

- 5.5 The PBAC noted that the resubmission offered a 12% price reduction, which together with the above amendments resulted in an ICER of \$155,000 to < \$255,000 per QALY gained. The PBAC noted that the resubmission additionally proposed that end-of-life costs be incorporated into the model and that this resulted in a substantially reduced ICER of \$55,000 to < \$75,000 per QALY gained. Use of the ITT population to inform the efficacy estimates further reduced the ICER to \$15,000 to < \$25,000 per QALY gained.
- 5.6 The PBAC noted the end-of-life cost was applied on a per cycle basis to patients in the post progression health state, and as patients in the cabozantinib arm were in this health state for a shorter period of time, the end-of-life cost for patients treated with cabozantinib was lower than for patients treated with placebo. The PBAC considered this lacked face validity. The PBAC did, however, consider that there would be monitoring and treatment costs for patients in the post progression state that would be dependent on the time spent in the health state, and that removing all of these costs was an extreme scenario. The PBAC noted that if a cost of approximately \$1 was applied per cycle to the post progression health state, that the ICER was less than \$95,000 to < \$115,000 per QALY gained. When the ITT population was used to inform efficacy, the ICER was less than \$95,000 to < \$115,000 per QALY gained with a post progression per cycle cost of approximately \$1. The PBAC noted the post progression costs were highly uncertain, but in the context of the costs of the treatments used post cabozantinib as presented in the November 2023 submission, and given the small patient numbers and total cost, it was reasonable to incorporate such a cost in the economic model. Hence, the PBAC considered that cabozantinib would be cost-effective at the price proposed in the submission.
- 5.7 The PBAC noted that the early re-submission made the requested changes to the utilisation estimates and that when the proposed 12% price reduction included, the revised estimated net cost to the PBS/RPBS was \$0 to < \$10 million over the first 6 years of listing. The PBAC considered that the revised estimates were acceptable.
- 5.8 The PBAC considered that the revisions to the requested restriction were acceptable. Specifically, the PBAC agreed that the addition that patients must have thyroid stimulating hormone adequately suppressed was appropriate and that patients should have a WHO performance status of no greater than 2. The PBAC also considered that the restriction be age agnostic.
- 5.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for cabozantinib:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies as the magnitude of the OS benefit was uncertain;

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- b) The treatment is expected to address a high and urgent unmet clinical need because there are no alternative treatment options for locally advanced or metastatic differentiated thyroid cancer;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

5.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Add new listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBAC item number	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOZANTINIB					
20 mg tablet, 30 40 mg tablet, 30 60 mg tablet, 30	NEW	1	30	2	Cabometyx, Ipsen Pty Ltd

Concept ID	Category / Program: Section 85 (General Schedule)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method: <input checked="" type="checkbox"/> Streamlined
	Severity: Locally advanced or metastatic
	Condition: Differentiated thyroid carcinoma
	PBS Indication: Locally advanced or metastatic differentiated thyroid carcinoma
	Treatment phase: Initial treatment
	Clinical criteria:
	The condition must be refractory to radioactive iodine; or
	Patient must be deemed ineligible for treatment with radioactive iodine,
	AND
	Clinical criteria:
	Patient must have progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) whilst on treatment with a vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor (TKI) for this indication;
	OR
	Patient must have developed intolerance of a severity necessitating permanent treatment withdrawal, in the absence of disease progression, to prior VEGF-targeted TKI therapy
	AND
	Clinical criteria:
	Patient must have a WHO performance status of not higher than 2,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND

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	Clinical criteria:
	Patient must have thyroid stimulating hormone adequately suppressed
	Prescribing instructions: Radioactive iodine refractory is defined as: <ul style="list-style-type: none"> • a lesion without iodine uptake on a radioactive iodine (RAI) scan; or • having received a cumulative RAI dose of greater than or equal to 600 mCi; or • progression within 12 months of a single RAI treatment; or • progression after two RAI treatments administered within 12 months of each other
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special Pricing Arrangements apply
	Note: Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all targeted 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.
	Note: Vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor's (TKI) include: lenvatinib

MEDICINAL PRODUCT medicinal product pack	PBAC item number	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOZANTINIB					
20 mg tablet, 30 40 mg tablet, 30 60 mg tablet, 30	NEW	1	30	5	Cabometyx, Ipsen Pty Ltd

	Category / Program: Section 85 (General Schedule)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method: <input checked="" type="checkbox"/> Streamlined
	Severity: Locally advanced or metastatic
	Condition: Differentiated thyroid carcinoma (DTC)
	PBS Indication: Advanced or metastatic differentiated thyroid carcinoma
	Treatment phase: Continuing treatment
	Clinical criteria:
	The condition must be refractory to radioactive iodine; or
	Patient must be deemed ineligible for treatment with radioactive iodine,
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Clinical criteria:
	Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST).
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised

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	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special Pricing Arrangements apply
	Note: Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all targeted 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.

Concept ID	Category / Program: Section 85 (General Schedule)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method: <input checked="" type="checkbox"/> Streamlined
	Severity: Locally advanced or metastatic
	Condition: Differentiated thyroid carcinoma (DTC)
	PBS Indication: Locally advanced or metastatic differentiated thyroid carcinoma
	Treatment phase: Grandfather supply
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date];
	AND
	Clinical criteria:
	The condition must be refractory to radioactive iodine; or
	Patient must be deemed ineligible for treatment with radioactive iodine,
	AND
	Clinical criteria:
	Patient must have had progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) whilst on treatment with a vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor (TKI) prior to receiving this drug for this indication;
	OR
	Patient must have developed intolerance of a severity necessitating permanent treatment withdrawal, in the absence of disease progression, to prior VEGF-targeted TKI therapy prior to receiving this drug for this indication
	AND
	Clinical criteria:
	Patient must have a WHO performance status of not greater than 2 prior to receiving this drug for this indication
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Clinical criteria:
	Patient must have thyroid stimulating hormone adequately suppressed
	Prescribing instructions:
	Radioactive iodine refractory is defined as: <ul style="list-style-type: none"> • a lesion without iodine uptake on a radioactive iodine (RAI) scan; or • having received a cumulative RAI dose of greater than or equal to 600 mCi; or • progression within 12 months of a single RAI treatment; or • progression after two RAI treatments administered within 12 months of each other
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised

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	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special Pricing Arrangements apply
	Note: Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all targeted 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.
	Note: Vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor's (TKI) include: lenvatinib

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

7 Context for Decision

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

8 Sponsor's Comment

The sponsor had no comment.