6.02 CABOZANTINIB, Tablet 20 mg, Tablet 40 mg, Tablet 60 mg, Cabometyx®, IPSEN PTY LTD

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (STREAMLINED) listing for the treatment of unresectable locally advanced or metastatic well- or moderately-differentiated pancreatic neuroendocrine tumour (pNET) or extra-pancreatic neuroendocrine tumour (epNET) after prior systemic therapy.

1.2 The evaluation and the ESC considered that the submission's proposed place in therapy for cabozantinib was not entirely clear. The submission's clinical management algorithm and financial estimates suggested the submission was requesting PBS listing of cabozantinib for pNET and epNET at the third line setting, pNET at the fourth line and beyond setting (referred to as fourth line herein), and epNET at the fourth line setting.

1.3 For the listing of cabozantinib in the third line setting in pNET, the listing was requested on the basis of a cost-minimisation approach (CMA) versus sunitinib.

1.4 For the listing of cabozantinib in the third line setting in epNET, the listing was requested on the basis of a CMA versus chemotherapy.

1.5 For the listing of cabozantinib in the fourth line setting in both pNET and epNET, the listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC) (represented by placebo).

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

Component	Description
Population	Adult patients with progressive pNET and epNET after prior systemic therapy
Intervention	Cabozantinib 60 mg orally once daily until disease progression or unacceptable toxicity.
Comparator	pNET - Sunitinib / Everolimus - Best supportive care (BSC) epNET - Chemotherapy - BSC
Outcomes	Progression free survival (PFS), objective response rate (ORR), overall survival (OS) and safety
Clinical claim	pNET - Compared to sunitinib / everolimus, comparable effectiveness, different but manageable safety profile. - Compared to BSC, superior effectiveness and inferior but manageable safety. epNET - Compared to chemotherapy, comparable effectiveness, different but manageable safety profile. - Compared to BSC, superior effectiveness and inferior but manageable safety.

Source: Table 1-1, p18 of the submission.
BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; EVE: everolimus; pNET: pancreatic neuroendocrine tumour; SUN: sunitinib
Note: The submission's nominated comparators depended on the place of therapy. While the place of therapy was not clearly described by the submission, the submission's clinical management algorithm (p32) and financial estimates (p215), suggested the submission was requesting cabozantinib at the third line and fourth line setting.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process to be reviewed under Project Orbis. At the time of PBAC consideration, the TGA Delegate's Overview was available.

2.2 The proposed indication as stated in the draft product information) was:

"[cabozantinib] is indicated for the treatment of adult patients with previously treated, locally advanced/unresectable or metastatic, well- or moderately-differentiated pancreatic neuroendocrine tumours (pNET) or extra-pancreatic neuroendocrine tumours (epNET)."

2.3 In the TGA Delegate's Overview, the TGA Delegate's preliminary view was to approve cabozantinib as follows:

"[cabozantinib] is indicated for the treatment of adult patients with locally advanced/unresectable or metastatic, well-differentiated extra-pancreatic (epNET) or pancreatic (pNET) neuroendocrine tumours who have progressed on at least one prior systemic therapy other than a somatostatin analogue".

2.4 The delegate stated, "This wording of the indication is preferred ... as it better reflects the inclusion criteria of CABINET and the intended treatment population (i.e. patients who have received/ are receiving a somatostatin analogue and have progressed on everolimus or [peptide receptor radionuclide therapy] PRRT (or another systemic

therapy). A favourable benefit-risk profile of cabozantinib in patients with advanced well-differentiated [neuroendocrine tumours] NETS has not been established as yet for those who have not progressed on any prior systemic therapy other than an [somatostatin analogue] SSA". The sponsor agreed to the proposed wording.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
CABOZANTINIB – initial					
Cabozantinib, 60mg tablet, 30	$9,472.60 published price $[redacted] effective price	1	30	2	Ipsen Pty Ltd
Cabozantinib, 40mg tablet, 30		1	30	2	Ipsen Pty Ltd
Cabozantinib, 20mg tablet, 30		1	30	2	Ipsen Pty Ltd
CABOZANTINIB – continuing					
Cabozantinib, 60mg tablet, 30	$9,472.60 published price $[redacted] effective price	1	30	5	Ipsen Pty Ltd
Cabozantinib, 40mg tablet, 30		1	30	5	Ipsen Pty Ltd
Cabozantinib, 20mg tablet, 30		1	30	5	Ipsen Pty Ltd

Source: Table 1-4 & 1-5, p34 & 35 of the submission.
Notes: Published and effective prices relate to the price proposed under a special pricing arrangement (SPA).
The effective price was an indication-based price, determined by the submission from the economic evaluation of the four requested populations and by weighting the proportion of patients with pNET and epNET.
The submission requested a flat pricing across doses, i.e. a flat price was requested across all strengths of cabozantinib tablets.
Prices calculated use PBS fees and markups effective 1/1/25.

Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Severity: Metastatic or unresectable
Condition: Neuroendocrine tumours (NETs)
Indication: Neuroendocrine tumours (NETs)
Treatment Phase: Initial
Clinical criteria:
The condition must be unresectable locally advanced or metastatic well-or moderately-well differentiated disease,
AND
Patient must have progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) whilst on treatment with prior treatment for this indication, OR Patient must have developed intolerance of a severity necessitating permanent treatment withdrawal, in the absence of disease progression, to prior treatment,
AND
The condition must be World Health Organisation (WHO) grade 0, 1 or 2.
Treatment criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:
Patient must be aged 18 years or older

Source: Table 1-5, p35 of the submission.

Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Severity: Metastatic or unresectable
Condition: Neuroendocrine tumours (NETs)
Indication: Neuroendocrine tumours (NETs)
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to (TBC – PBS listing date); OR Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Patient must have stable or responding disease according to Response Evaluation Criteria in Solid Tumours (RECIST),
AND
Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug.
Treatment criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:
Patient must be aged 18 years or older

Source: Table 1-6, p35 of the submission.

3.1 The requested restriction was for NETs with a clinical criterion that "the condition must be unresectable locally advanced or metastatic well-or moderately-well differentiated disease" and for the patient to have progressive disease while on prior treatment (or be intolerant to prior treatment). Restriction criterion specific to the target population (i.e. pNET or epNET), or line of therapy (third or fourth line) was not requested.

3.2 The submission requested a single weighted price, based on indication-specific prices that were weighted by the proportion of patients with pNET and epNET across the third- and fourth-line settings. This is discussed further in the 'Weighted price' section.

3.3 The submission proposed flat pricing (i.e. the same price for all strengths of cabozantinib) and requested an effective dispensed price for maximum quantity (DPMQ) of $ for 30 tablets. In the pre-PBAC response the sponsor reduced the requested DPMQ to $ for 30 tablets.

3.4 The evaluation noted that the requested restriction was inconsistent with the restrictions for the nominated comparators for pNET, sunitinib and everolimus. Notable differences included:

- The inclusion of "locally advanced" disease for cabozantinib. As only three (3.2%) patients in the pNET cohort and no patients in the epNET cohort of the CABINET trial had locally advanced disease, the efficacy of cabozantinib in this subgroup was unclear. Moreover, the submission did not include locally advanced patients in the financial estimates. The Pre-Sub-Committee Response (PSCR) clarified that locally advanced patients were not intended to form part of the requested population;

- The inclusion of "moderately-well differentiated" for cabozantinib. Only four (4.2%) patients in the pNET cohort and 11 (5.4%) patients in the epNET cohort had moderately differentiated disease; therefore, the evaluation considered the efficacy of cabozantinib in this subgroup to be unclear. The PSCR stated that the sponsor was amenable to removing the words "moderately-differentiated" from the proposed restriction, which would align with changes to the international nomenclature which has adopted the WHO classification of poor- or well-differentiated;
- The criterion of "progressive disease while on prior treatment" for cabozantinib does not specify what prior treatment should include, whereas the sunitinib or everolimus restriction specifies "patient must be symptomatic (despite somatostatin analogues (SSAs)) or patient must have disease progression". The PSCR) stated that it would be reasonable to include the following criterion in the proposed restriction: "Patient must be symptomatic (despite treatment with somatostatin analogues), or patient must have disease progression; and
- A "WHO grade 0, 1 or 2" for cabozantinib was proposed, whereas none was specified for sunitinib or everolimus. The WHO Classification of Endocrine and Neuroendocrine Tumours is a universal definition system for neuroendocrine neoplasia based on differentiation and proliferative grading, and ranges from grades 1-3 but does not include '0', contrary to the requested restriction. The sponsor was asked to clarify the WHO grade in the requested listing. The PSCR did not clarify this.

3.5 Under the current PBS restrictions for sunitinib and everolimus, patients who have progressive disease with either of these therapies are no longer eligible to continue treatment with the drug, and no sequential use is allowed between the two drugs post-progression (i.e. patients who progress on sunitinib are not eligible to receive PBS subsidised everolimus and vice versa). To align with the submission's proposed treatment algorithms and comparators, the existing PBS restrictions for sunitinib and everolimus in pNET would need to be amended to preclude the use of sunitinib or everolimus following progression on cabozantinib. This would align with use of these therapies in the CABINET trial, where sunitinib and everolimus use was permitted prior to cabozantinib.

3.6 Based on the requested restriction, as long as patients have developed progressive disease whilst on prior treatment for this indication, a patient could commence treatment with cabozantinib multiple times. The PSCR proposed that the restriction be updated to include the criterion: "Treatment is restricted to one course per patient per lifetime for this condition". The ESC considered this was appropriate.

3.7 The requested restriction allows for treatment of a different patient population than enrolled in the CABINET trial. Differences include:

- The CABINET trial enrolled patients who had an Eastern Cooperative Oncology Group (ECOG) performance score of 0-2. An ECOG score was not included in the requested restriction. The PSCR did not support inclusion of an ECOG performance status in the listing criteria for cabozantinib as it is not included in the existing listings for sunitinib or everolimus;
- In CABINET, patients must have had disease progression after receiving (or having intolerance leading to treatment discontinuation of) at least one line of therapy, not including SSAs, whereas this was not specified in the restriction. The ESC noted that the restriction would allow for treatment in patients who have not progressed on everolimus, sunitinib or PRRT, which was inconsistent with the evidence provided (refer to paragraph 4.8).The PBAC considered that the restriction should be revised to require patients to have progressed on at least one prior systemic therapy other than a SSA to reflect the updated indication wording proposed in the TGA Delegate's Overview; and
- The requested restriction stated that cabozantinib must be the sole PBS-subsidised therapy. However, concomitant SSAs were permitted in CABINET with 35 (55%) and 92 (69%) patients randomised to the cabozantinib arm in the pNET and epNET cohorts, respectively, having concurrent SSA use. If the PBAC were to allow concomitant use of cabozantinib and SSAs, then the evaluation considered that flow-on changes would be required to the existing SSA listings (the current listings for SSAs state these must be the sole PBS-subsidised therapy for this condition (GEP-NET)). The PSCR supported the removal of the requirement for cabozantinib to be the sole PBS-subsidised therapy, and also supported flow-on changes to the SSAs to allow concurrent use with cabozantinib.

3.8 No formal grandfathering of patients was proposed by the submission, but the submission noted that there is a private market program through which at least two patients were self-funding cabozantinib for NETs, at the time of submission. The requested restriction wording was intended to accommodate transition to PBS funded therapy for these patients.

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

4 Population and disease

4.1 Neuroendocrine Neoplasms (NENs) are a group of heterogeneous tumours with complex presentations. Classification of NENs is based on grade, differentiation and other pathological factors. Clinically, NENs broadly comprise two subgroups, NETs and neuroendocrine carcinomas (NECs) (Pavel 2020, Das and Dasari 2021); these subgroups have vastly different prognoses and survival rates (Pavel 2020). Well-differentiated NETs have a better prognosis than poorly differentiated NECs and

develop slowly over several years. Australian data show that NETs represent approximately 42% of all NENs (Australian Institute of Health and Welfare (AIHW) 2025) affecting fewer than 1 in 5,000 Australians and are considered a rare cancer (Neuroendocrine Cancer Australia 2025). NETs are often indolent at onset with a prolonged disease course and lower risk of distant metastasis. However, their prognosis is highly dependent on location, stage, grade, histopathology and functional status and this varies significantly between and within subpopulations (Oronsky 2017, Pavel 2020).

4.2 Most NETs of the gastrointestinal (GI) tract occur in the midgut, which includes small intestine (SI) NETs, appendiceal NETs and ascending colon NETs. Collectively, in the literature, NETs of the pancreas are referred to as pancreatic (pNET) while all NETs outside of the pancreas (e.g. GI NETs, lung NETs and other/unknown NET locations) are extra-pancreatic NETs (epNETs). NETs of the pancreas (i.e. pNET) or GI tract (i.e. a type of epNET) are also collectively referred to as gastroenteropancreatic NETs (GEP-NETs). The target population of the submission are patients with pNETs and epNETs, both of which have distinct molecular genetics and are associated with different prognoses. The PBAC previously considered sunitinib for patients with pNET (recommended at the August 2013 PBAC meeting) and everolimus (recommended at the March 2014 PBAC meeting). While the PBAC has not previously considered a submission specifically for patients with epNET, functional carcinoid tumour and non-functional GEP NETs (subset of epNET) were considered by the PBAC in its consideration of somatostatin analogues (SSAs) lanreotide (recommended at the July 2005 and November 2017 PBAC meeting respectively) and octreotide (recommended prior to July 2005 and recommended at the July 2019 PBAC meeting respectively).

4.3 Survival rates for patients with NENs vary widely based on disease stage, primary tumour site, and tumour grade (Pape 2008, Yao 2008, Ozaslan 2016, Sakin 2018, Panzuto 2023). A large-scale observational study of 14,834 NET and NEC patients from the National Cancer Registration and Analysis Service (NCRAS) in England (2012–2018) demonstrated that survival rates declined significantly with advancing disease stage. Fewer than 25% of patients with Stage IV (distant metastatic) NETs survived beyond five years, compared to over 75% of those diagnosed with Stage I or II disease, and over 50% of those with Stage III disease (White 2022). Survival rates also vary based on the primary tumour site. An analysis of UK NCRAS registry data (White 2022) found that five-year survival rates for Stage IV NETs were below 30% for primary tumours originating in the lung (12%), colon (18%), stomach (21%), rectum (22%), and pancreas (26%). In contrast, five-year survival rates were comparatively higher in other GI NET locations: caecum (48%), small intestine (43%), and appendix (42%).

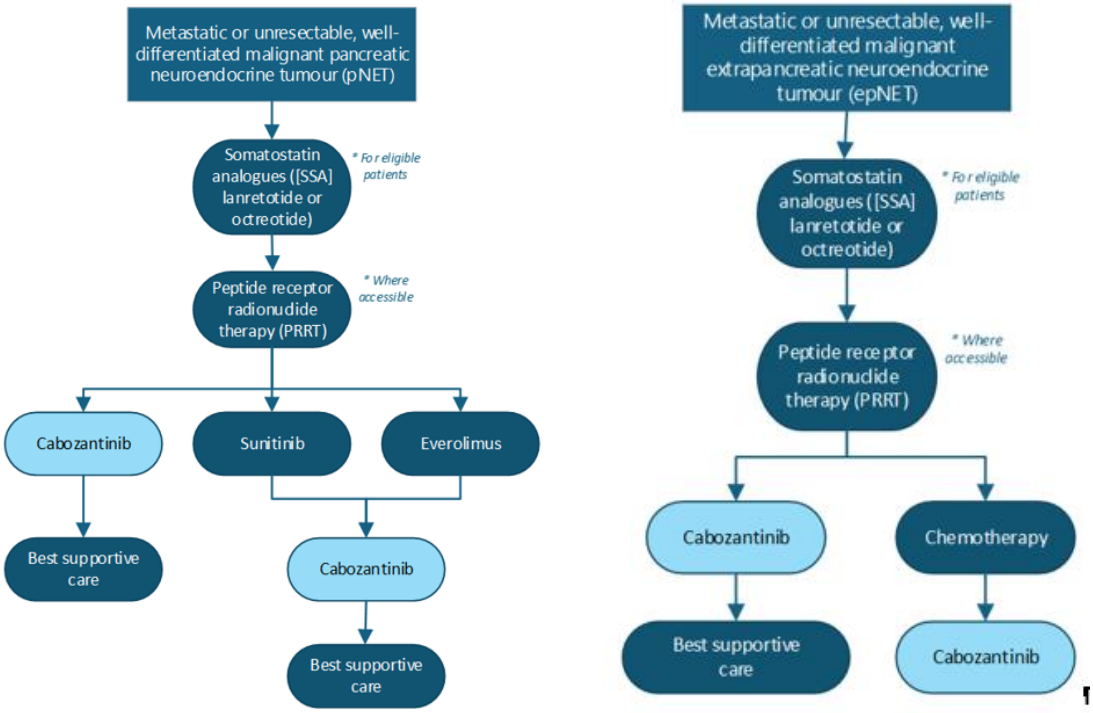
4.4 The target population was adult patients with previously treated, locally advanced, unresectable, or metastatic well- or moderately differentiated NETs. The submission further claimed that there was evidence for the efficacy of cabozantinib in patients

with progressive disease after treatment with prior therapies and consequently requested the allowance of sequential treatment with cabozantinib.

4.5 Figure 1 shows the submission's proposed algorithm for the pNET (left) and epNET (right) settings. The evaluation and the ESC considered that the basis for these algorithms was unclear as the submission did not provide complete descriptions or sources. Despite acknowledging the complexity of the disease, the algorithms did not consider the clinical suitability of patients (primary site, grade, Ki-67 index) and eligibility for treatment on the PBS, specific to the Australian clinical landscape.

4.6 Whilst the submission considered that PRRT was 'second line' therapy in its algorithm, in the MSAC consideration of 177 Lu-DOTA-octreotate, a form of PRRT for advanced NETs and other high somatostatin receptor expressing tumours, PRRT was proposed as an add-on therapy rather than a replacement for comparator management strategies (p24, MSAC 1744 Public Summary Document (PSD), August and November 2024 meeting). Overall, the lines of therapy in pNET and epNET do not appear to be clear cut.

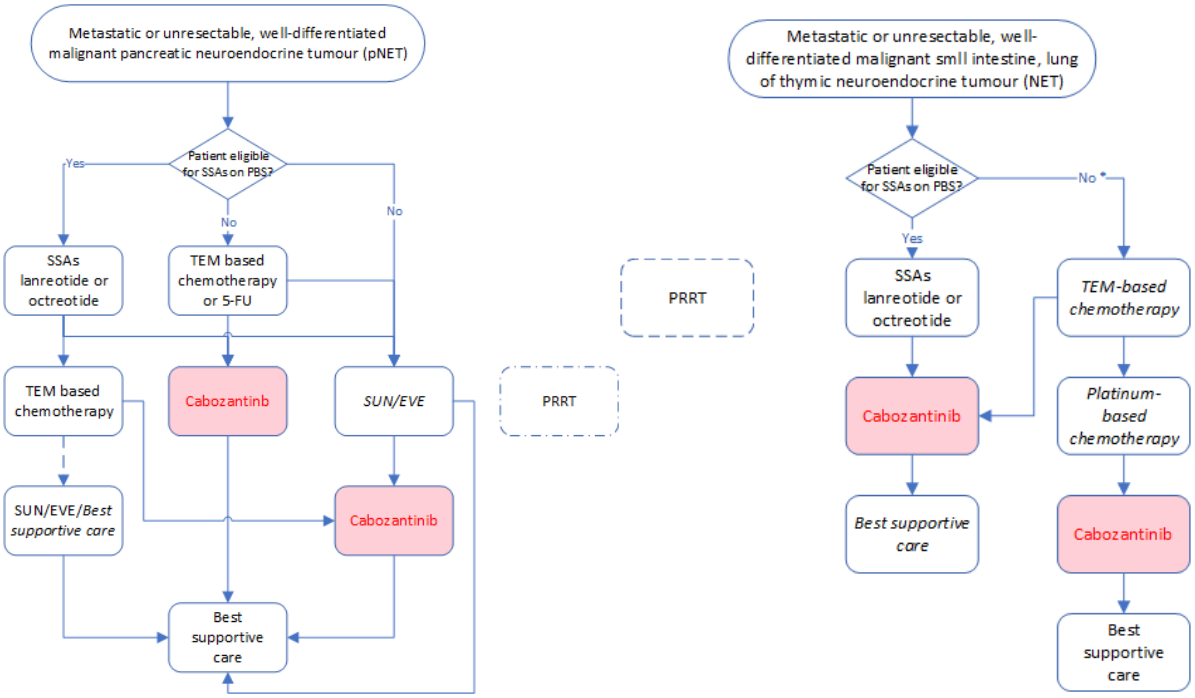
Figure 1: Clinical management algorithms proposed by the submission for pNET (left) and epNET (right)



Source: Figures 1-3 & 1-4, p32 of the submission.

4.7 Clinical management algorithms (constructed during evaluation) showing the place in therapy encompassed by the submission's proposed restriction are in Figure 2.

Figure 2: Clinical management algorithm enabled by submission's proposed restriction in pNET (left) and epNET (right); constructed during the evaluation)



Source: Constructed during the evaluation based on the ESMO guidelines for GEP NENs, ESMO guidelines for lung and thymic carcinoids, COSA guidelines for NENs; PBS restrictions and 1744 MSAC PSD.

5-FU: Fluorouracil; COSA: Clinical Oncology Society of Australia; ESMO: European Society for Medical Oncology; EVE: everolimus; GEP: gastroenteropancreatic; SUN: sunitinib; NEN: Neuroendocrine Neoplasms; PRRT: peptide receptor radionuclide therapy; SSAs: somatostatin analogues; TEM: temozolomide

Note: The dotted outline indicates no fixed line of therapy for PRRT given "treatment with 177 Lu-DOTA-octreotate should not be viewed as a fixed line in any patient's therapy" (p20, MSAC 1744 PSD, August and November 2024 MSAC meeting).

pNET: The dotted arrow to SUN/EVE indicates treatment with SUN/EVE following chemotherapy is not restricted on the PBS, although this was not included in the ESMO algorithm (following SSAs)

* epNET: EVE is included as a treatment option in the ESMO guidelines and is TGA approved for non-functional NET of gastrointestinal or lung origin but is not PBS listed for these conditions.

For G2 NETs with a Ki-67 index of 15%-20% or that are significantly progressive carcinoids: chemotherapy may be considered. ESMO guidelines (Baudin 2021a) recommended alkylating-based chemotherapy as first-line chemotherapy and platinum-based chemotherapy as second-line chemotherapy.

For G3 NETs (not included in the requested PBS population), the choice chemotherapy may be based on Ki-67 index: TEM-based chemotherapy is suggested as first-line chemotherapy followed by platinum-based /etoposide chemotherapy for Ki-67 index of 22-55%; and vice versa for NETs with a Ki-67 index >55%.

Italics indicate the submission's nominated comparator(s); note that chemotherapy crosses multiple lines of therapy.

4.8 Whilst referred to as the third- and fourth line settings, the evaluation and the ESC noted that the submission's requested restriction would allow patients to receive cabozantinib after progression on only one line of previous treatment (i.e. second line or beyond), as depicted in Figure 2. This would include allowing use immediately after first-line SSA therapy, which is consistent with the NCCN guidelines but earlier than in the CABINET trial, where patients were required to have progressed whilst on prior treatment with everolimus, sunitinib or PRRT. However, as outlined in paragraph 7.21, the PBAC noted that the TGA Delegate had proposed to register cabozantinib for use in 'patients who had progressed on at least one prior systemic therapy other than a

somatostatin analogue' which would result in a treatment algorithm more similar to that outlined in Figure 1 (i.e. the algorithm proposed by the submission).

4.9 Further, in the pivotal CABINET trial, patients with pNET in the cabozantinib and placebo arm had a median of three (range: 1-8) and two (range: 1-7) prior systemic anti-cancer regimens (excluding SSAs) respectively. For patients with epNET, this was a median of two (range: 1-5) and two (range: 1-6) for the cabozantinib and placebo arms respectively. There was a considerable range regarding the number of prior therapies received by patients in CABINET and the line of therapy was unclear (SSAs may also count as a line of therapy in the Australian setting); as such, the evaluation considered that the comparator may also be uncertain. Moreover, the evaluation noted that if the line of therapy in the PBS population differs the trial this may represent an applicability issue. Overall, the ESC noted the trial population represented a heavily pre-treated group of patients, while the submission's proposed restriction would allow use as early as second-line. Refer to paragraph 7.20 for the PBAC's consideration.

4.10 Cabozantinib is an orally administered, third-generation small molecule that inhibits the enzymatic activity of multiple tyrosine kinases. Cabozantinib has a unique mechanism of action by targeting RTKs including VEGFR2, RET, MET, and AXL which are implicated in tumour growth, angiogenesis and cancer cell invasion or metastasis (Sennino 2013, Krampitz 2016, and Reuther 2016). Cabozantinib is currently PBS listed for the treatment of stage IV RCC, and locally advanced or metastatic DTC.

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

5 Comparator

5.1 For the treatment of pNET in the third line setting, the submission nominated sunitinib and everolimus as the main comparators. The main arguments provided in support of this nomination were that cabozantinib would likely substitute treatment with other Tyrosine Kinase Inhibitor (TKI) targeted therapies. Sunitinib and everolimus are PBS listed for the treatment of metastatic or unresectable, well-differentiated malignant pNET.

5.2 For the treatment of pNET in the fourth line setting (i.e. sequential treatment with cabozantinib after progression on sunitinib or everolimus), the submission nominated BSC (which the submission described as 'no further active treatment') as a comparator. Sunitinib or everolimus were not considered as fourth line setting comparators as the submission appeared to propose that use of sunitinib or everolimus would not be permitted following progression on cabozantinib (given the existing restrictions do not permit sequential use of everolimus and sunitinib). However, the evaluation noted that if sequential treatment with sunitinib or everolimus after progression on cabozantinib for pNET were allowed then the comparator in the fourth line setting would be sunitinib or everolimus.

5.3 For the treatment of epNET in the third line setting, the submission nominated chemotherapy as the main comparator. The submission did not specify the type of chemotherapy; but based on the submission's search strategy it was assumed to comprise capecitabine and temozolomide (CAPTEM) or temozolomide (TEM)-based regimens and folinic acid, fluorouracil and oxaliplatin (FOLFOX) or oxaliplatin-based regimens. The main argument provided in support of this nomination was that chemotherapy would likely be the most used therapy and therefore the most likely to be replaced. It was unclear whether sunitinib or everolimus are used privately for the treatment of epNET in Australia.

5.4 For the treatment of epNET in the fourth line setting (i.e. sequential treatment with cabozantinib after progression on chemotherapy), the submission nominated BSC (which the submission described as 'no further active treatment') as a comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented a clinical perspective on treatment of patients with NETs, noting that the heterogeneity of patient and tumour characteristics (e.g. in terms of site of origin, performance status, organ function, Ki-67 proliferation index, somatostatin receptor expression) and other factors (e.g. access to PRRT) impact the treatment options available to each patient. The clinician noted that whilst several treatments for NETs are available, SSAs are not appropriate for all patients, and access to PRRT is limited to tertiary centres. The clinician stated that optimal sequencing of treatments is not well defined, and that whilst chemotherapy is a potential option for some patients with epNET, not all patients are suitable for chemotherapy and some patients respond poorly. The clinician highlighted that there is a significant need for additional lines of treatment. In response to the Committee's questions, the clinician stated that the proportion of patients who receive systemic therapy depends on the site of the NET. The clinician also outlined that the likely proportion of use of cabozantinib in the third- versus fourth-line settings in clinical practice would be difficult to predict. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon group of diseases.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (2) and organisations (Rare Cancers Australia, NeuroEndocrine Cancer Australia, and the Medical Oncology Group of Australia (MOGA)) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cabozantinib including improved progression free survival (PFS),

quality of life, and fewer cancer-related symptoms (such as fatigue, nausea and abdominal pain). The comments highlighted the limited treatment options available for patients with pNETs and the very limited options available for patients with epNET. One individual indicated that despite trying eight therapies and participating in trials, they experienced disease progression or serious side effects, however since starting cabozantinib their symptoms had reduced significantly in terms of both frequency and intensity. The PBAC noted that this advice was supportive of the evidence provided in the submission.

6.3 NeuroEndocrine Cancer Australia also highlighted the need to broaden indication coverage for medicines that treat rare and less common cancers including neuroendocrine cancer, and stated its preference for cabozantinib to be made available as a first-line treatment given the high risk of side effects associated with chemotherapy.

6.4 The MOGA also expressed its strong support for the cabozantinib submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the CABINET trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for cabozantinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with placebo.

Clinical trials

6.5 In the third line setting, no head-to-head trials comparing cabozantinib and the nominated comparators (sunitinib and everolimus for pNET; chemotherapy for epNET) were available.

6.6 An indirect treatment comparison (using placebo as the common comparator) was used to assess the submission's claim of non-inferior efficacy to sunitinib and everolimus for the treatment of pNET. The indirect treatment comparison was based on the following three trials:

- CABINET (NCT03375320): Cabozantinib vs placebo (pNET cohort);
- A618-1111 (NCT00428597): Sunitinib vs placebo; and
- RADIANT-3 (NCT00510068): Everolimus vs placebo.

The PBAC previously considered A618-1111 and RADIANT-3 in its consideration of sunitinib and everolimus (recommended at the August 2013 and March 2014 PBAC meeting, respectively).

6.7 The submission did not identify any relevant trials for the treatment of epNET with chemotherapy; evidence for the efficacy of chemotherapy was based on 11 retrospective chart reviews. An unanchored indirect comparison of cabozantinib

[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

versus chemotherapy (CAPTEM or FOLFOX) was presented to support the claim of non-inferior efficacy to chemotherapy; however, the retrospective studies identified also included TEM-based and oxaliplatin-based chemotherapy regimens.

6.8 In the fourth line setting where BSC was the nominated comparator (for both pNET and epNET), the submission's claim of superior efficacy was based on one head-to-head randomised trial comparing cabozantinib and placebo (used as a proxy for BSC): CABINET.

6.9 Details of the trials and studies presented in the submission are provided in Table 2.

Table 2: Trials/studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
CABINET (NCT03375320)	Randomized, Double-Blinded Phase III Study of Cabozantinib versus Placebo in Patients with Advanced Neuroendocrine Tumours after Progression on Prior Therapy (CABINET)	Clinical Study Report A021602, 21 May 2024
	Chan, J. A et al. Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumours	New England Journal of Medicine 2024
A618-1111 (NCT00428597)	Raymond, E et al. Sunitinib malate for the treatment of pancreatic neuroendocrine Tumours	N Engl J Med 2011; 364(6): 501-513
	Raymond, E et al. Evidence of activity and clinical benefit with sunitinib in patients with pancreatic neuroendocrine Tumours (NET)	Annals of oncology 2010; 21(Suppl 6):13
	Vinik, A et al. Patient-Reported Outcomes and Quality of Life with Sunitinib Versus Placebo for Pancreatic Neuroendocrine Tumours: Results From an International Phase III Trial	Targeted oncology 2016; 11(6): 815-824.
	Faivre, S et al. Sunitinib in pancreatic neuroendocrine Tumours: updated progression-free survival and final overall survival from a phase III randomized study	Ann Oncol 2017; 28(2): 339-343.
	Fazio, N et al. Updated Efficacy and Safety Outcomes for Patients with Well-Differentiated Pancreatic Neuroendocrine Tumours Treated with Sunitinib	Target Oncol 2021; 16(1): 27-35.
	Valle, J. W et al. Sunitinib In Patients With Pancreatic Neuroendocrine Tumours: Update of Safety Data	Future Oncology 2019; 15(11): 1219-1230.
RADIANT-3 (NCT00510068)	Yao, J. C et al. Everolimus for advanced pancreatic neuroendocrine Tumours	N Engl J Med 2011; 364(6): 514-523.
	Ito, T et al. Everolimus for Advanced Pancreatic Neuroendocrine Tumours: A Subgroup Analysis Evaluating Japanese Patients in the RADIANT-3 Trial	Japanese Journal of Clinical Oncology 2012; 42(10): 903-911.
	Lombard-Bohas C et al. Impact of prior chemotherapy use on the efficacy of everolimus in patients with advanced pancreatic neuroendocrine Tumours: a subgroup analysis of the phase III RADIANT-3 trial	Pancreas 2015; 44(2): 181-9.
	Yao JC et al. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumours: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study	J Clin Oncol 2016; 34(32): 3906-3913.
Chemotherapy (non-randomised studies)	Owen, DH et al. Combination therapy with capecitabine and temozolomide in patients with low and high grade neuroendocrine tumors, with an exploratory analysis of O6-methylguanine DNA methyltransferase as a biomarker for response. doi: 10.18632/oncotarget.22001	Oncotarget; 2017; 24; 8(61): 104046-104056.
	Thomas, K et al. Outcomes of Capecitabine and Temozolomide (CAPTEM) in Advanced Neuroendocrine Neoplasms (NENs). doi: 10.3390/cancers12010206	Cancers (Basel); 2020; 14;12(1): 206.

Study ID	Protocol title/ Publication title	Publication citation
	Spada, F et al. Oxaliplatin-Based Chemotherapy in Advanced Neuroendocrine Tumors: Clinical Outcomes and Preliminary Correlation with Biological Factors. doi: 10.1159/000444087	Neuroendocrinology; 2016; 103(6): 806-14
	Robelin, P et al. Characterization, Prognosis, and Treatment of Patients With Metastatic Lung Carcinoid Tumors. doi: 10.1016/j.jtho.2019.02.002	J Thorac Oncol. 2019; 14(6): 993-1002.
	Girot, P et al. Oxaliplatin and 5-fluorouracil (FOLFOX) in advanced well-differentiated digestive neuroendocrine tumors: A multicenter national retrospective study from the French Group of Endocrine Tumors (GTE). DOI:10.1200/JCO.2019.37.15_suppl.4104	JCO; 2019; 37: 4104-4104.
	Al-Toubah, T et al. Efficacy and Toxicity Analysis of Capecitabine and Temozolomide in Neuroendocrine Neoplasms	J Natl Compr Canc Netw 2021; 20(1): 29-36.
	Crespo, G et al. Capecitabine and Temozolomide In Grade 1/2 Neuroendocrine : A Spanish Multicenter Experience	Future Oncology 2016; 13(7): 615-624
	Chatzellis, E et al. Activity and Safety of Standard and Prolonged Capecitabine/Temozolomide Administration in Patients with Advanced Neuroendocrine Neoplasms	Neuroendocrinology 2019; 109(4): 333-345
	Al-Toubah T et al. Capecitabine and Temozolomide in Advanced Lung Neuroendocrine Neoplasms. doi: 10.1634/theoncologist.2019-0361	Oncologist; 2020; 25(1): e48-e52.
	Papaxoinis, G et al. Capecitabine and Temozolomide in Patients with Advanced Pulmonary Carcinoid Tumours	Neuroendocrinology 2019; 110(5): 413-421
	Faure, M et al. Systemic chemotherapy with FOLFOX in metastatic grade 1/2 neuroendocrine cancer	Mol Clin Oncol 2017; 6(1): 44-48

Source: Tables 2-4 & 2-5, p43, 45 & 46 of the submission.

6.10 The key features of the trials are summarised in Table 3.

Table 3: Key features of the included trials (pNET and epNET)

Study	N	Design/duration	Risk of bias	Relevant comparison	Population	Primary outcomes
CABINET	298 [a]	Phase 3, R, DC, PC, crossover allowed [b]	Low	Cabozantinib 60mg PO daily Placebo daily	pNET and epNET	PFS by BICR
A618-1111	171	Phase 3, R, DB, PC, crossover allowed [c]	Low	Sunitinib 37.5mg daily PO + BSC Placebo daily + BSC	pNET	PFS by IA
RADIANT-3	410	Phase 3, R, DB, PC, crossover allowed [d]	Low	Everolimus 10mg daily PO + BSC Placebo daily + BSC	pNET	PFS by IA

Source: Table 2-15, p66 of the submission.

BICR: blinded independent central review; BSC: best supportive care; DB: double blind; epNET: extra-pancreatic neuroendocrine tumour; IA: investigator assessment; PC: placebo controlled; PFS: progression free survival; pNET: pancreatic neuroendocrine tumour; PO: orally; R: randomised

[a] pNET: N=95 (n=64 patients randomised to cabozantinib and n=31 patients randomised to placebo); epNET: N=203 (n=134 patients randomised to cabozantinib and n=69 patients randomised to placebo)

[b] Patients received study treatment until disease progression, unacceptable toxicity or withdrawal of consent. Upon disease progression confirmed by central radiology review, those who were receiving placebo were unblinded and could elect to crossover to open-label therapy with cabozantinib.

[c] Treatment continued until RECIST-defined progression was documented, unacceptable adverse events occurred, or the patient died. Patients with disease progression while receiving placebo could enter an open-label sunitinib extension protocol (NCT00443534), or a continuation study (NCT00428220).

The trial was terminated early because of the risk of serious adverse events, disease progression, and death among patients receiving placebo.

[d] Treatment continued until progression of the disease, development of an unacceptable toxic effect, drug interruption for 3 weeks or longer, or withdrawal of consent. Patients who had been assigned to placebo and subsequently met the criteria for disease progression according to RECIST, were given the choice to switch to open label everolimus.

6.11 The pivotal CABINET trial provided clinical information on the efficacy and safety of cabozantinib in the treatment of NETs. The CABINET trial was used by the submission in:

- The indirect comparison (using placebo as the common comparator) to sunitinib (A618-1111) and everolimus (RADIANT-3) (in the third line setting for pNET);
- The comparison to chemotherapy (in the third line setting for epNET); and
- As a head-to-head trial for the pNET and epNET population (in the fourth line setting).

6.12 CABINET was a US-based, multicentre, randomised (2:1), double-blind, placebo-controlled trial that evaluated the efficacy, safety and tolerability of cabozantinib in patients with progressive pNET or epNET, whose disease had progressed after at least one prior FDA-approved therapy (everolimus, sunitinib or Lu-177 DOTATATE). If patients were taking SSAs they were allowed to continue them so long as they had been on a stable dose for at least 2 months prior. Patients in this trial were enrolled into two separate cohorts - one for pNET and one for epNET. Upon disease progression confirmed by central radiology review, treatment allocation was unblinded, and placebo treated patients could crossover to open-label cabozantinib.

6.13 The CABINET trial was terminated early under recommendation by the Data and Safety Monitoring Board (DSMB), as significant improvement in PFS by investigator assessment (IA) was observed for patients receiving treatment with cabozantinib compared with placebo. Enrolment to the trial stopped on 7th August 2023. At this time, 200 of a target of 210 patients had been enrolled in the epNET cohort and 95 of a target of 185 patients had been enrolled in the pNET cohort. Primary efficacy and safety analyses were performed based on a data cutoff date of 24 August 2023, which corresponded to the date of study-wide unblinding and when all placebo patients were eligible to cross over to cabozantinib.

6.14 For the treatment of pNET in the third line setting, a number of differences at baseline were noted between the patient populations enrolled in each of the included trials in relation to: the number of treatments previously received; duration of disease; ECOG performance score; proportion of patients with non-functional tumours; proportion of patients with concomitant SSAs; and proportion of patients previously treated with SSAs. The submission noted that the first patients were enrolled in the A618-1111 and RADIANT-3 in 2007, when the landscape of available treatments for NETs was more limited, primarily including SSAs. Comparatively, when CABINET commenced in 2018, the therapeutic landscape had started to expand, with options including sunitinib and everolimus. This was reflected in the previous treatments received by patients enrolled in the trials; in CABINET, 80% of patients had prior systemic treatment with everolimus whereas patients in A618-1111 and RADIANT-3 primarily received SSAs or chemotherapy. Therefore, the patient population and the composition of BSC may not

be comparable between the included trials. This also poses an applicability issue for using the results from CABINET as evidence in the third line setting for pNET, as patients in the Australian setting are not expected to have had prior therapy with sunitinib or everolimus at the place in therapy proposed for cabozantinib. The PSCR acknowledged this issue but outlined that prior therapy with everolimus, 177-Lu-DOTATATE, sunitinib (pNET only) or SSAs was not identified as a significant treatment effect modifier (refer to paragraph 6.31).

6.15 Given the number of potential sources of transitivity and exchangeability issues across the included trials, the submission appropriately concluded that on balance, the transitivity assumptions required to conduct a Bucher indirect treatment comparison (ITC) across the pivotal randomised controlled trials could not be met. Therefore, a formal ITC was not considered informative. The submission noted that in the consideration of everolimus for the treatment of pNET at the November 2012 PBAC meeting, the comparability of patients between the sunitinib and everolimus trials was noted as a concern by PBAC, and a matching-adjusted indirect comparison (MAIC) was later presented in a resubmission (i.e. at the PBAC March 2014 meeting, when everolimus was recommended for listing). The submission claimed that consideration was given to the feasibility of conducting an anchored MAIC or simulated treatment comparison of the pNET cohort from CABINET and the A618-1111 or RADIANT-3 data, however, the extent of the differences in the baseline characteristics, the small patient numbers in the CABINET pNET cohort and the lack of access to individual patient data from the CABINET trial were all significant hurdles to conducting a robust anchored comparison. The submission noted that results of the ITC were presented "strictly for completeness". As such, the evaluation considered that the basis of the claim for comparable effectiveness was unclear. The PSCR stated that the lack of access to individual patient data limited the analyses that could be conducted and therefore, the claim in the third line pNET patient population was based on the naïve side by side comparison, presented in the submission. The PSCR further stated that the Bucher ITC was presented in the interest of transparency as a "what if" analysis to demonstrate that the clinical claim was likely to be reasonable.

6.16 For the treatment of epNET in the third line setting, 11 non-randomised studies (retrospective chart reviews) were selected by the submission to inform the efficacy of systemic chemotherapy. The patient population and the number of patients included in these studies are summarised in Table 4. Given the studies were retrospective observational studies with the lack of a comparative group, the risk of bias should be considered high. The PSCR acknowledged the limitations of this data, but outlined that epNET is a rare condition with limited therapeutic options.

Table 4: Summary of non-randomised studies (chemotherapy; epNET)

Study ID	N	Population	PD measure
TEM-based regimens			
Al-Toubah 2021	462	All patients with advanced NET seen between Jan 2008 and Jun 2019, who received treatment with CAPTEM. pNET in 71%	Chart review (not RECIST)
Thomas 2020	116	NEN patients who received at least one cycle of CAPTEM between November 2010 and June 2018 and had at least one follow up visit. 91% of patients had received prior treatment. 69/116 (59%) had non-pNEN	RECIST
Al-Toubah 2019	20	Patients with metastatic lung NENs who received treatment with CAPTEM between Jan 2008 and Sept 2018. Patients with SCLC were excluded. Patients without further visits at the centre were also excluded. Fourteen (70%) had typical lung NETs, five had (25%) atypical carcinoids, and one (5%) had disease defined as a large-cell neuroendocrine carcinoma.	RECIST
Chatzellis 2019	79	Locally advanced, unresectable, or metastatic NENs who received at least one cycle of CAPTEM from June 2007 to February 2018 were identified in 3 European Neuroendocrine Tumour Society (ENETS) certified NEN referral centres in Greece, Poland and Israel. Pancreas n=30 (38%); GI-NEN n=15 (19%)	RECIST
Papaxoinis 2019	33	Patients with histologically or cytologically confirmed pulmonary carcinoid tumours. Treatment-naïve or were diagnosed with radiological progressive disease. Treated with CAPTEM between March 2014 to August 2018.	RECIST
Owen 2017	38	Advanced neuroendocrine carcinomas of all grades and both pancreatic and non-pancreatic origin: pNET was the most common primary tumour location (61%); followed by the lung (8%); rectum (8%); and unknown (8%). 55% received prior cytotoxic or targeted agents and 55% had received at least 1 local therapy.	RECIST
Crespo 2016	65	Patients with metastatic or primary unresectable NETs who received systemic chemotherapy with CAPTEM at the Departments of Medical Oncology of 12 referral hospitals throughout Spain between June 2009 and August 2015. 19 patients (29%) had a diagnosis of epNET. Remaining 71% were pNET.	RECIST
Robelin 2019	162 [a]	Metastatic disease with histologically confirmed carcinoid tumour with primary lung origin. Consecutive patients presenting between Nov 1995 and Jun 2017.	RECIST
Oxaliplatin-based regimens			
Girot 2019	149	All patients with advanced well-differentiated digestive NETs treated with at least 3 cycles of FOLFOX between 2004 and 2018 in 12 centres of the French GTE. pNET n=88; SI NET n=37; stomach n=7; rectum n=4; unknown n=13	RECIST
Faure 2017	31	Confirmed diagnosis of progressive NET, locally advanced or metastatic, well differentiated, G1/G2. pancreas n=14; GI n=3; lung n=8; unknown n=6	RECIST
Spada 2016	78	Patients consecutively treated with oxaliplatin-based therapy from 1999 to 2013 selected from the NET databases of 5 Italian referral centres with particular expertise in the treatment of these rare tumours. pancreas n=46; GI n=24; lung n=19; unknown 10%	RECIST
Robelin 2019	162 [a]	Metastatic disease with histologically confirmed carcinoid tumour with primary lung origin. Consecutive patients presenting between Nov 1995 and Jun 2017.	RECIST

Source: Table 2-19, pp77-80 of the submission.

CAPTEM: capecitabine and temozolomide; epNET: extra-pancreatic neuroendocrine tumour; FOLFOX: leucovorin/fluorouracil/oxaliplatin; GI: gastrointestinal; epNET: extra-pancreatic neuroendocrine tumour; NET: neuroendocrine tumour; NEN: neuroendocrine neoplasm; pNEN: pancreatic neuroendocrine neoplasm; pNET: pancreatic neuroendocrine tumour; PD: progressive disease; RECIST = Response evaluation criteria in solid tumours; TEM: temozolomide

[a] N=58 received TEM-based chemotherapy and N=84 received oxaliplatin-based chemotherapy

6.17 The reporting of baseline characteristics differed between the included chemotherapy studies, making it difficult to assess the comparability of the patient populations. Primary disease site was the only characteristic consistently reported across all the

studies, and even so, this varied largely between studies. Eight out of the 11 studies included patients with pNET (range: 38%-71%), while the remaining three studies only enrolled patients with NETs of primary lung origin. As such, the patient population included in the clinical evaluation for the treatment of epNET in the third line setting may not reflect the requested PBS population and as such represented a potential applicability issue.

6.18 Overall, the comparison of baseline characteristics of patients included in the non-randomised chemotherapy studies were not informative, and there was poor exchangeability and transitivity between the included studies.

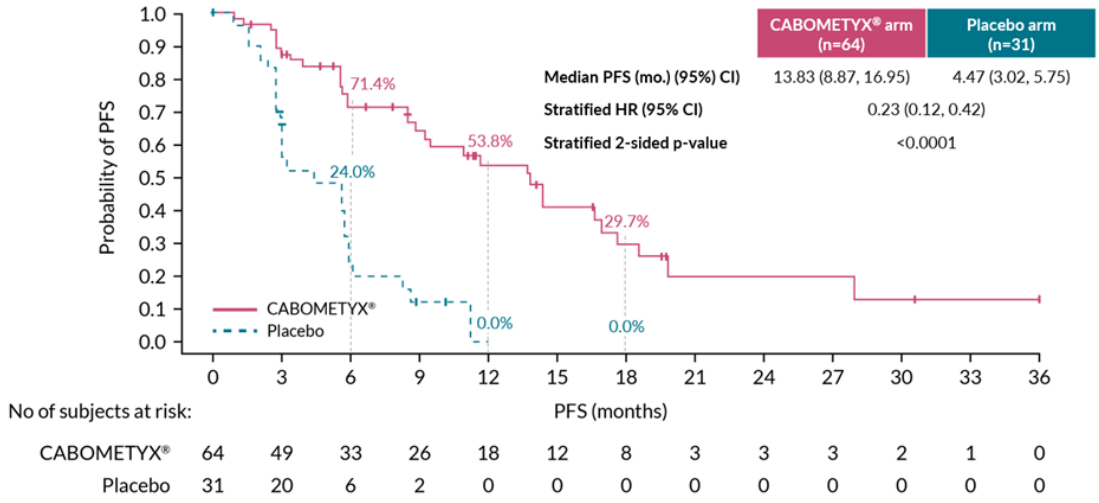
6.19 The submission's clinical efficacy claims were made based on the outcomes of PFS and overall survival (OS).

Comparative effectiveness

Direct comparison (CABINET; fourth line pNET and epNET)

6.20 Figure 3 and Figure 4 show the PFS Kaplan-Meier (KM) results of the CABINET trial, for the pNET and epNET cohorts respectively (data cutoff date: 24 August 2023). Table 5 summarises the PFS statistics by blinded independent central review (BICR) and by IA for the pNET and epNET cohorts.

Figure 3: KM plot of PFS by BICR in CABINET (pNET cohort; ITT population)



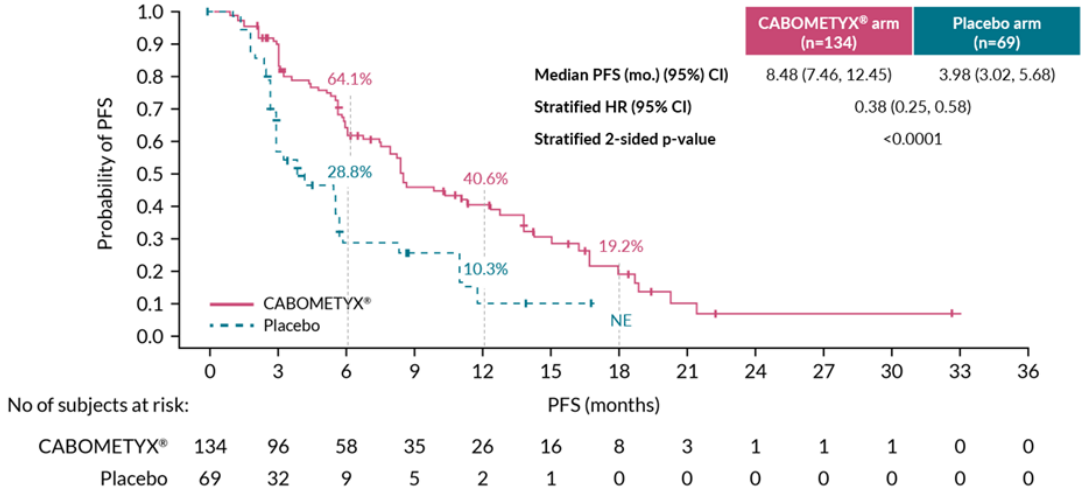
Source: 2-7, p80 of the submission.

BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; LR: log-rank test; pNET: pancreatic neuroendocrine tumour; OPEN: Oncology Patient Enrolment Network.

Note: DCO: 24th August 2023

A bold pink or blue dash indicates a censored observation in the cabozantinib or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months. Stratification factors for pNET: 1. Concurrent SSA Use (Yes, No) and 2. Prior sunitinib therapy (Yes, No). Stratification was per OPEN criteria

Figure 4: KM plot of PFS by BICR in CABINET (epNET cohort; ITT population)



Source: Figure 2-22, p104 of the submission.
BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; LR: log-rank test; OPEN: Oncology Patient Enrolment Network.
Note: DCO: 24th August 2023
A bold pink or blue dash (– or |) indicates a censored observation. The grey dotted lines and associated percentages indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months.
Stratification factors for epNET: 1. Concurrent SSA Use (Yes, No) and 2. Primary Site (Midgut/Unknown vs Non-midgut GI/Lung/Other). Stratification was per OPEN criteria.

Table 5: PFS (by BICR and by IA) in CABINET (pNET and epNET; ITT population)

	pNET		epNET	
	CBZ (N=64)	**PBO (N=31)**	**CBZ (N=134)**	**PBO (N=69)**
PFS by BICR				
Number of patients, n (%)				
Event	32 (50)	25 (81)	71 (53)	40 (58)
Death	7 (11)	4 (13)	18 (13)	5 (7.2)
Documented progression	25 (39)	21 (68)	53 (40)	35 (51)
Median PFS (95% CI), months	13.83 (8.87,16.95)	4.47 (3.02, 5.75)	8.48 (7.46, 12.45)	3.98 (3.02, 5.68)
Stratified HR (95% CI) [a]	0.23 (0.12, 0.42)		0.38 (0.25, 0.58) [b]	
P value	<0.0001		<0.0001	
PFS by IA				
Number of patients, n (%)				
Event	39 (61)	24 (77)	83 (62)	51 (74)
Death	5 (7.8)	1 (3.2)	18 (13)	6 (8.7)
Documented progression	34 (53)	23 (74)	65 (49)	45 (65)
Median PFS (95% CI), months	10.97 (8.41,13.86)	3.06 (2.86, 5.91)	8.38 (5.98, 11.07)	3.25 (2.99, 5.42)
Stratified HR (95% CI) [a]	0.29 (0.16, 0.52)		0.41 (0.28, 0.60)	
P value	<0.0001		<0.0001	

Source: Tables 2-20, 2-21 & 2-39, pp80, 83 & 103 of the submission & Tables 18, 19, 35 & 36, pp85, 87 124, 126 of the CSR.
BICR: blinded independent central review; CBZ: cabozantinib; CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; IA: investigator assessment; ITT: intent-to-treat; K-M, Kaplan-Meier; PBO: placebo; pNET, pancreatic neuroendocrine tumour
Note: p-values are from log-rank test.
Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].
[a] Hazard ratios were calculated from Cox proportional hazards model.

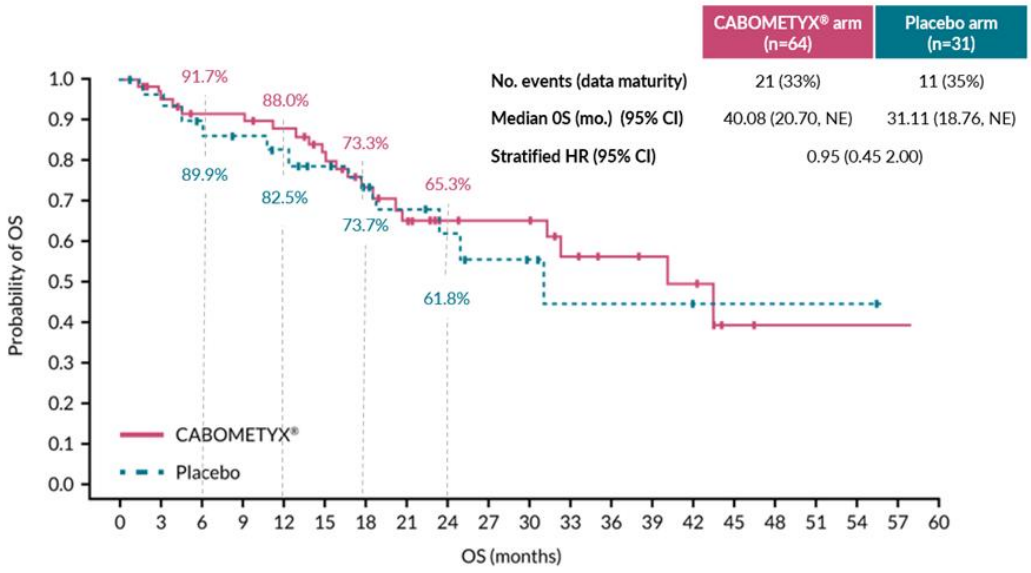
[b] Erroneously reported by the submission as 0.38 (0.25, 0.59), updated based on Table 18, p85 of the submission.

6.21 In the pNET cohort, patients randomised to cabozantinib reported a 77% lower risk of disease progression or death, on average, compared to patients randomised to placebo (PFS by BICR HR=0.23; 95% CI: 0.12, 0.42). The KM estimate of median PFS by BICR was 13.83 months (95% CI: 8.87, 16.95) in the cabozantinib arm compared with 4.47 months (95% CI: 3.02, 5.75) in the placebo arm, an estimated 9.36-month difference between treatment arms. The separation between the cabozantinib curve and placebo curve was maintained at landmarks of 6, 12 and 18 months. Results of PFS by IA (HR=0.29; 95% CI: 0.16, 0.52) were less favourable than PFS by BICR but the direction was consistent with the primary outcome of PFS by BICR assessment.

6.22 In the epNET cohort, patients randomised to cabozantinib reported a 62% lower risk of disease progression or death, on average, compared to patients randomised to placebo (PFS by BICR HR=0.38; 95% CI: 0.25, 0.58. The KM estimate of median PFS by BICR was 8.48 months (95% CI: 7.46, 12.45) in the cabozantinib arm compared with 3.98 months (95% CI: 3.02, 5.68) in the placebo arm, an estimated 4.5-month difference between treatment arms. The separation between the cabozantinib curve and placebo curve was maintained at landmarks of 6 and 12 months. Results of PFS by IA (HR=0.41; 95% CI: 0.28, 0.60) were less favourable than PFS by BICR but the direction was consistent with the primary outcome of PFS by BICR assessment.

6.23 Figure 5 and Figure 6 show the OS KM results for the pNET and epNET cohorts respectively, of the CABINET trial (data cutoff date: 24 August 2023) without any adjustment for crossover. Table 6 summarises the OS statistics for the pNET and epNET cohorts.

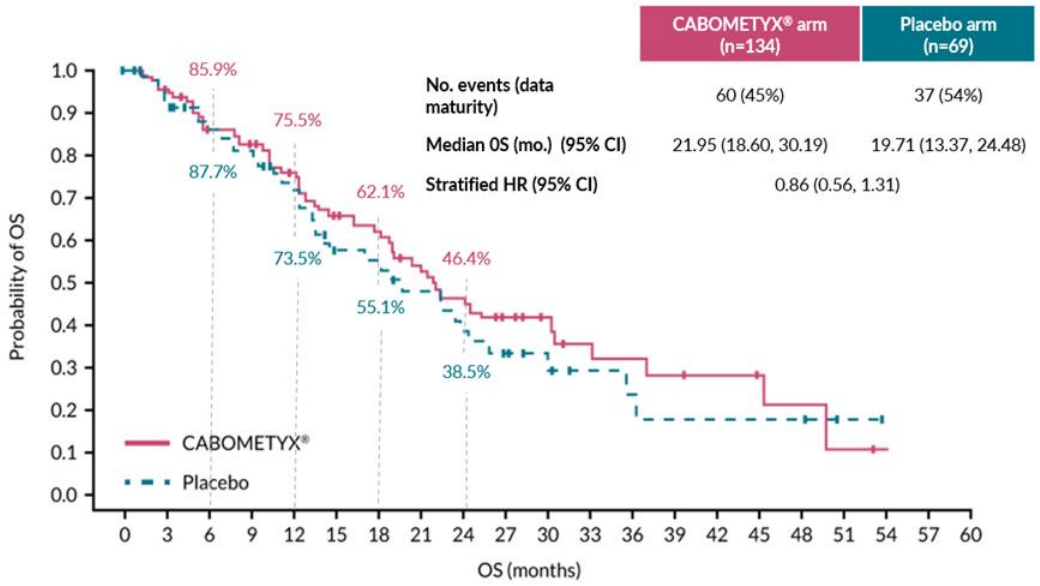
Figure 5: KM plot of OS in CABINET (pNET cohort; ITT population)



Source: Figure 2-16, p90 of the submission. CI: confidence interval; DCO: data cut-off; HR: hazard ratio; ITT: intent-to-treat; LR: log-rank test; OPEN: Oncology Patient Enrolment Network; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Note: DCO: 24th August 2023
A bold pink or blue dash indicates a censored observation in the CABOMETYX® or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months.
Stratification factors for pNET: 1. Concurrent SSA Use (Yes, No) and 2. Prior sunitinib therapy (Yes, No). Stratification was per OPEN criteria.

Figure 6: KM plot of OS in CABINET (epNET cohort; ITT population)



Source: Figure 2-25, p108 of the submission.
CI: confidence interval; DCO: data cut-off; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; ITT: intent-to-treat; KM: Kaplan-Meier; LR: log-rank test; OPEN: Oncology Patient Enrolment Network; OS: overall survival.
Note: DCO: 24th August 2023
A bold pink or blue dash indicates a censored observation in the CABOMETYX® or placebo arm, respectively. The grey dotted lines and associated percentages for each treatment arm indicate the KM landmark estimates of percent of patients event-free at 6, 12 or 18 months.
Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs Non-midgut GI/Lung/Other]. Stratification was per OPEN criteria.

Table 6: OS in CABINET (pNET and epNET; ITT population)

	pNET		epNET	
	CBZ (N=64)	PBO (N=31)	CBZ (N=134)	PBO (N=69)
Number of patients, n (%)				
Censored	43 (67)	20 (65)	74 (55)	32 (46)
Alive	39 (61)	20 (65)	67 (50)	30 (43)
Death after data cutoff date	4 (6.3)	0	7 (5.2)	2 (2.9)
Event: death	21 (33)	11 (35)	60 (45)	37 (54)
Median OS (95% CI), months	40.08 (20.70, NE)	31.11 (18.76, NE)	21.95 (18.60, 30.19)	19.71 (13.37, 24.48)
Stratified HR (95% CI) [a]	0.95 (0.45, 2.00)		0.86 (0.56, 1.31)	
P value	0.8852		0.4871	

Source: Tables 2-20 & 2-39, pp80 & 103 of the submission and Tables 21 & 38, p91 & 131 of CSR

CBZ: cabozantinib; CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; ITT: intent-to-treat; NE: not estimable; pNET: pancreatic neuroendocrine tumour; PBO: placebo

Note: p-values are from log-rank test.

Stratification factors for pNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Prior Sunitinib Therapy (Yes, No).

Stratification factors for epNET: 1. Concurrent Somatostatin Analog Use (Yes, No) and 2. Primary Site [Midgut/Unknown vs. Non-midgut GI/Lung/Other].

[a] Hazard ratios were calculated from Cox proportional hazards model.

6.24 In the pNET cohort, 33% of patients (n=21) randomised to cabozantinib and 35% of patients (n=11) randomised to placebo had died by the data cutoff. The submission noted a total of 12 patients in the placebo arm (39%) crossed over to receive cabozantinib; these patients were not censored at the time of crossover and were analysed under the arm to which they were randomised (i.e. placebo) for OS under ITT principles. The point estimate of OS HR was 0.95 (95% CI: 0.45, 2.00) and was not statistically significant.

6.25 In the epNET cohort, 45% of patients (n=60) randomised to cabozantinib and 54% of patients (n=37) randomised to placebo had died. The submission noted that in the placebo arm, 29% of patients (n=20) crossed over to receive cabozantinib; these patients were not censored at the time of crossover and were analysed under the arm to which they were randomised (i.e. placebo) for OS under ITT principles. The point estimate of OS HR was 0.86 (95% CI: 0.56, 1.31) and was not statistically significant.

6.26 The submission claimed that the interpretation of OS data was limited due to the crossover design of the CABINET trial, and the immaturity of OS data at the time of clinical trial termination. Given the degree of crossover, the submission presented results adjusted for treatment switching using the rank-preserving structural failure time modelling (RPSFTM) and inverse probability of censoring weights (IPCW) methods.

6.27 Table 7 summarises the HRs of cabozantinib versus placebo obtained for OS from the ITT analysis and crossover adjustment analyses. It was noted that sensitivity analyses adjusting for the effect of crossover based on a RPSFTM were reported in the CSR for CABINET (separate to the analysis conducted by the submission). Results for these were extracted during the evaluation and presented in Table 7 for comparison. No statistically significant difference was observed between cabozantinib and placebo for

OS (based on a nominal significance level of 0.05), even after crossover adjustment. The IPCW method produced numerically more favourable results for cabozantinib.

Table 7: OS HRs (95% CI) for cabozantinib vs placebo with and without crossover adjustment

Measure	ITT Analysis	SA: RPSFTM	RPSFTM (without recensoring)		IPCW [a]	
			inflated SE	naïve SE	untruncated	truncated
pNET						
Stratified HR (95% CI)	0.95 (0.45, 2.00); p=0.8852	0.86 (0.41, 1.79); p=0.6820 [b]	0.89 (0.19, 4.17)	0.89 (0.43, 1.87)	0.74 (0.36, 1.52)	0.74 (0.36, 1.52)
Unstratified HR (95% CI)	0.88 (0.42, 1.83)	-	0.85 (0.33, 2.15)	0.85 (0.41, 1.76)	0.72 (0.32, 1.65)	0.72 (0.32, 1.65)
epNET						
Stratified HR (95% CI)	0.86 (0.56, 1.31); p=0.4871	0.81 (0.53, 1.23); p=0.3205 [c]	0.84 (0.52, 1.37)	0.84 (0.55, 1.29)	0.65 (0.39, 1.07)	0.64 (0.39, 1.05)
Unstratified HR (95% CI)	0.86 (0.57, 1.29)	-	0.85 (0.55, 1.30)	0.85 (0.56, 1.28)	0.66 (0.41, 1.06)	0.65 (0.40, 1.04)

Source: Table 2-62, p132 of the submission.

epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT: intention to treat; RPSFTM: rank-preserving structural failure time model; SA: sensitivity analysis; SE: standard error.

Note: p-values were not reported for the unstratified HR for the ITT analysis, and not reported by the analysis conducted by the submission.

[a] HRs presented for IPCW are adjusted HRs from a Cox marginal structural model including all baseline covariates adjusted for as part of the weight estimation as covariates.

[b] Appeared to be based on the stratified HR, results extracted based on p133 of the CSR.

[c] Appeared to be based on the stratified HR, results extracted based on p94 of the CSR.

6.28 The IPCW (untruncated) HR was used in the submission's economic model.

6.29 Objective response rate (ORR) was also reported in CABINET. In the pNET cohort, a significant improvement in ORR in patients randomised to cabozantinib compared to patients randomised to placebo (at a nominal significance level of 0.05) was found, with a confirmed ORR treatment difference of 18.8% (95% CI: 9.2%, 28.3%; p-value= 0.0115). However, when assessed by IA, the observed ORR for the cabozantinib arm of the trial was reduced (from 18.8% to 7.8%) and the confirmed ORR treatment difference between the cabozantinib vs placebo did not reach significance (7.8%; 95% CI: 1.2%, 14.4%; p=0.1218).

6.30 In the epNET cohort, a confirmed ORR treatment difference of 5.2% (95% CI: 1.5%, 9.0%; p-value= 0.0524) was reported. This was not significant based on the nominal significance level of 0.05. The confirmed ORR treatment difference was further reduced when assessed by IA (2.3%; 95% CI: -2.0%, 6.6%; p=0.3652).

6.31 The effect of patient baseline characteristics and stratification was explored in subgroup analyses of the BICR-assessed analyses of PFS of CABINET.

- For the pNET cohort in CABINET, tests for interaction conducted during the evaluation suggested that prior sunitinib or 177-Lu-DOTATATE use, and concurrent SSA treatment were not treatment effect modifiers, though results may have been limited by the small sample sizes.

- Tests for interaction conducted during the evaluation for the epNET cohort suggested the concurrent use of SSAs, prior treatment with everolimus or 177-Lu-DOTATATE were not treatment effect modifiers, though results may have been limited by the small sample size. Notably, the upper bound of the 95% CI included '1' for patients with an ECOG of 0, patients with tumour primary site of non-midgut GI/lung/other, patients with ≥3 prior systemic therapies or patients with tumour grade 3, and the treatment benefit between cabozantinib and placebo in these subgroups was uncertain.
- In both pNET and epNET, due to the small sample size, the HR was not applicable in patients with an ECOG of 2 and patients with moderately differentiated tumours. However, patients with moderately differentiated tumours were included by the submission as part of the requested PBS population, and patients were not limited by ECOG in the requested restriction. These may represent applicability issues.

6.32 Overall, in CABINET, patients treated with cabozantinib who were enrolled in the pNET cohort tended to perform better and had more favourable HRs in all categories compared to patients treated with cabozantinib who were enrolled in the epNET cohort.

Indirect treatment comparison (third line pNET)

6.33 Given the submission concluded that the transitivity assumptions required to conduct a Bucher ITC (using placebo as the common comparator) across the CABINET, A618-1111 and RADIANT-3 trials could not be met, the submission presented an indirect treatment comparison "strictly for completeness" (see Table 8). Comparative assessments of OS in the clinical evaluation presented by the submission were performed using the unadjusted data reported from the double-blind periods of the included trials.

Table 8: Summary of ITCs on PFS and OS in the included trials (pNET; ITT Population)

Trial	Comparison	Active trt n/N (%)	Placebo n/N (%)	HR (95% CI)
PFS by BICR				
CABINET	CBZ vs PBO	32/64 (50)	25/31 (81)	**0.23 (0.12, 0.42)**
A618-1111	SUN vs PBO	22/86 (26)	39/85 (46)	**0.32 (0.18, 0.55)**
RADIANT-3	EVE vs PBO	95/207 (46)	142/203 (70)	**0.34 (0.26, 0.44)**
ITC: CBZ vs SUN				0.72 (0.31, 1.66)
ITC: CBZ vs EVE				0.68 (0.34, 1.33)
ITC: EVE vs SUN				1.06 (0.57, 1.97)
PFS by IA				
CABINET	CBZ vs PBO	39/64 (61)	24/31 (77)	**0.29 (0.16, 0.52)**
A618-1111	SUN vs PBO	30/86 (35)	51/85 (60)	**0.42 (0.26, 0.66)**
RADIANT-3	EVE vs PBO	109/207 (53)	165/203 (81)	**0.35 (0.27, 0.45)**
ITC: CBZ vs SUN				0.69 (0.33, 1.46)
ITC: CBZ vs EVE				0.83 (0.44, 1.57)
ITC: EVE vs SUN				0.83 (0.50, 1.40)
OS, estimated from trials (reported in primary published papers Yao 2011; Raymond 2011)				
CABINET	CBZ vs PBO	21/64 (33)	11/31 (35)	0.95 (0.45, 2.00)
A618-1111	SUN vs PBO	9/86 (10)	21/85 (25)	**0.41 (0.19, 0.89)**
RADIANT-3	EVE vs PBO	51/207 (25)	50/203 (25)	1.05 (0.71, 1.55)
ITC: CBZ vs SUN				2.32 (0.79, 6.78)
ITC: CBZ vs EVE				0.9 (0.39, 2.1)
ITC: EVE vs SUN				2.56 (1.08, 6.08)
OS, 2nd analysis, used in OS ITC in Everolimus PSD (Nov 2012) [a]				
CABINET	CBZ vs PBO			0.95 (0.45, 2.00)
A618-1111	SUN vs PBO	34/86 (40)	39/85 (46)	0.74 (0.47, 1.17) [a]
RADIANT-3	EVE vs PBO			0.89 (0.64, 1.23) [a]
ITC: CBZ vs SUN				1.29 (0.54, 3.10)
ITC: CBZ vs EVE				1.07 (0.47, 2.41)
ITC: EVE vs SUN				1.21 (0.69, 2.12)

Source: Table 2-55, p124 of the submission.

CBZ: cabozantinib; EVE: everolimus; HR: hazard ratio; ITC: indirect treatment comparison; ITT: intent-to-treat; NE: not estimable; NR: not reported; OS: overall survival; PBO: placebo; SUN: sunitinib

[a] The submission based this ITC on the HRs used in the ITC for everolimus vs sunitinib. However, these values may not be reliable as the PBAC did not accept non-inferiority of everolimus and sunitinib based on this analysis.

Values in bold indicate significance.

6.34 Notably, the PFS in the common comparator arm (placebo) differed between the trials. Median PFS in the placebo arm was lowest in CABINET (3.06 months) and highest in A618-1111 (5.5 months). This was further evidence of the substantial transitivity issues between the studies.

Unanchored indirect comparison (third line epNET)

6.35 For the treatment of epNET in the third line setting, The submission presented a table with data for median PFS and median OS for cabozantinib from the CABINET trial and for TEM-based and oxaliplatin-based chemotherapy from the non-randomised chemotherapy studies; these were presented specifically for epNET patients, where available (see Table 9). The submission also presented a forest plot of the median PFS (Figure 7) and median OS (Figure 8).

Table 9: Median PFS and median OS from the non-randomised studies (epNET)

Study ID	Primary tumour site	Median PFS (months) [a] (95% CI)	Forest plot? [b]	Median OS (months) [a] (95% CI)	Forest plot? [c]
CABINET (CBZ arm)	epNET n=134	By BIRC: 8.48 (7.46, 12.45) By IA: 8.38 (5.98, 11.07)	Y	21.95 (18.60, 30.19)	Y
TEM-based regimens					
Owen 2017 (N=38)	pNET in 61%	All: 13.0 (5.6, 17.0) epNET: 8.4 (2.4, 13.3) pNET: 16.7 (6.1, 41.9)	N	All: 29.3 (17.7, 45.3) epNET: 18.5 (4.6, 32.6) pNET: 42.9 (18.5, NR)	N
Thomas 2020 (N=116)	non-pNEN n=69	non-pNEN: 11 (6-18)	Y	non-pNEN: 38 (30 - 46)	Y
Robelin 2019 (n=58)	lung	4.6 (3.0 - 5.7)	Y	25.0 (14.8 - 40.2)	Y
Al-Toubah 2022 (N=462)	pNET in 71%	All: 18 (14.0 - 21.9) pancreatic: 23 non-pancreatic: 10	N	All: 51 (42.8 - 59.2) pancreatic: 62 non-pancreatic: 28	N
Crespo 2017 (N=65)	epNET n=19	15.3 (7.4 - 23.2)	Y	41.6 (26.8 - 56.3)	Y
Chatzellis 2019 (N=79)	pancreas n=30 (38%); GI-NEN n=15 (19%)	pancreas: 23.5 (15.9 - 31.2) GI-NEN 6.4 (1.5 - 11.3)	Y	pancreas: 83.9 (-) GI-NEN: 13.4 (8.4 - 18.4)	Y
Al-Toubah 2019 (N=20)	lung	13 (4.4 - 21.6)	Y	68 (35.3 - 100.7)	Y
Papaxoinis 2020 (N=33)	lung	9 (3.3 - 14.7)	Y	30.4 (23.2-37.6) [d]	Y
Oxaliplatin-based regimens					
Robelin 2019 (n=84)	lung	9.3 (7.2 - 12.7)	Y	37.8 (29.6 - 45.2)	Y
Girot 2019 (N=149)	pNET n=88; SI NET n=37; stomach n=7; rectum n=4; unknown n=13	pNET: 9; SI NET: 9; stomach: 14; rectum: 4; unknown: 6	N	pNET: 30; SI NET: 28; stomach: 31; rectum: 25; unknown: 15	N
Faure 2017 (N=31)	pancreas n=14; GI n=3; lung n=8; unknown n=6	All: 14.1 (9.3, 24.1) No difference in PFS according to tumour location (p=0.995)	Y for all patients	NR	N
Spada 2016 (N=78)	pancreas n=46%; GI n=24%; lung n=19%; unknown n=10%	Pancreas: 0.81 years (0.63 - 1.10); lung 0.63 (0.23, 0.96); GI (0.46 (0.18, 0.88)	Y	Pancreas: 2.64 years (1.26, 4.17); lung: 1.77 (0.63, 3.86); GI 1.74 (0.79, -)	Y

Source: Table 2-43, pp111-112 of the submission.

BICR: blinded independent central review; CAPTEM: capecitabine and temozolomide; CBZ: cabozantinib; epNET: extra-pancreatic neuroendocrine tumour; GI: gastrointestinal; IA: investigator assessment; N: No; NET: neuroendocrine tumour; NR = not reached OS: overall survival; PFS: progression-free survival; pNEN: pancreatic neuroendocrine neoplasm; pNET: pancreatic neuroendocrine tumour; TEM: temozolomide; Y: yes

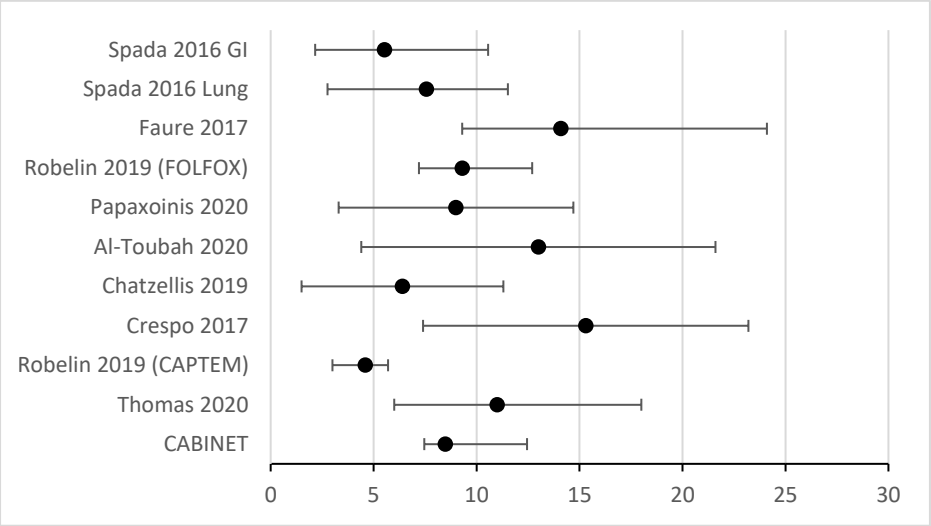
[a] In months unless otherwise indicated

[b] Whether or not the study was included in the submission's forest plot of median PFS

[c] Whether or not the study was included in the submission's forest plot of median OS

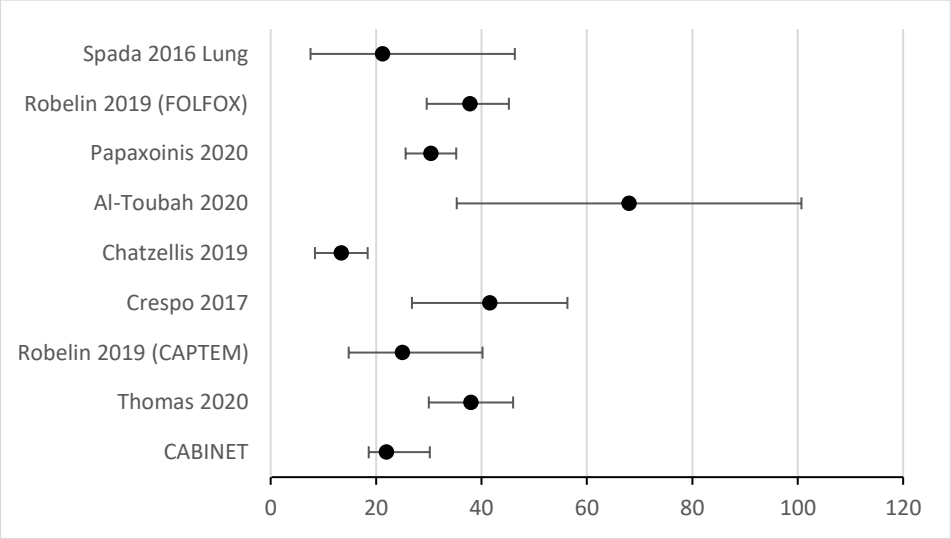
[d] The values reported by the submission (30.4 (25.6 - 35.2)) were for the subset of patients with complete histological data. This was updated for the whole population during the evaluation, based on the publication.

Figure 7: Forest plot of median PFS reported in the non-randomised studies and CABINET (months; epNET)



Source: Figure 2-27, p113 of the submission.
CAPTEM: CAPTEM: capecitabine and temozolomide; FOLFOX: folinic acid, fluorouracil and oxaliplatin; PFS: progression-free survival

Figure 8: Forest plot of median OS reported in the non-randomised studies and CABINET (months; epNET)



Source: Figure 2-28, p113 of the submission.
CAPTEM: capecitabine and temozolomide; FOLFOX: folinic acid, fluorouracil and oxaliplatin; OS: overall survival

6.36 The submission described that except for the temozolomide-treated patients in Robelin (2019), the median PFS observed for cabozantinib in the epNET cohort of CABINET was comparable with the available evidence for chemotherapies, notwithstanding the caveats of comparing outcomes from a prospective, interventional randomised trial with those from several, small retrospective chart reviews. The submission further described that median OS reported in epNET patients in the CABINET trial was less comparable to the non-randomised studies, however the OS data in CABINET were immature.

Comparative harms

Direct comparison (CABINET; fourth line pNET and epNET)

6.37 The submission claimed that cabozantinib for the treatment of pNET and epNET in the fourth ling setting, had an inferior but manageable safety profile compared to BSC. Safety results reported in CABINET were based on the data cutoff date of 24 August 2023 and referred to adverse events (AEs) occurring during the double-blind treatment phase. The safety observations in placebo-treated patients who crossed over to open-label cabozantinib after disease progression were reported separately. The CSR concluded that among the 32 total patients who crossed over in CABINET (12 patients from the placebo arm in the pNET cohort and 20 patients from the placebo arm in the epNET cohort), safety results were consistent with those from patients who received cabozantinib only.

6.38 A summary of safety outcomes reported in CABINET in the Safety population is provided in Table 10 and Table 11 for the pNET and epNET cohorts respectively. Regardless of cohort (pNET or epNET) or treatment arm (cabozantinib or placebo), all patients (100%) experienced an AE. Compared with the placebo arm, the cabozantinib arm in both cohorts had a higher proportion of patients with:

- AEs that were considered related to study treatment;
- Serious adverse events (SAEs);
- Grade 3 and/or 4 AEs; and
- AEs leading to dose modification

Table 10: Adverse event overview in CABINET (pNET; Safety population)

	CBZ only (n=63)	PBO (n=31)	RR	RD
AE	63 (100%)	31 (100%)	NE	0.00 (-0.06, 0.11)
Related AE	62 (98%)	26 (84%)	**1.17 (1.04, 1.46)**	**0.15 (0.04, 0.31)**
SAE	29 (46%)	7 (23%)	**2.04 (1.07, 4.22)**	**0.24 (0.03, 0.41)**
Related SAE	23 (37%)	2 (6.5%)	**5.66 (1.67, 21.06)**	**0.30 (0.13, 0.44)**
Worst Grade 3 or 4 AE	46 (73%)	14 (45%)	**1.62 (1.12, 2.56)**	**0.28 (0.07, 0.47)**
Worst Grade 3 or 4 Related AE	41 (65%)	7 (23%)	**2.88 (1.57, 5.83)**	**0.43 (0.22, 0.59)**
Worst Grade 4 AE	7 (11%)	0	7.50 (0.97, NE)	0.11 (-0.00, 0.21)
Worst Grade 4 Related AE	6 (9.5%)	0	6.50 (0.83, NE)	0.10 (-0.02, 0.19)
Worst Grade 5 AE	0 [a]	0	NE	0.00 (-0.11, 0.06)
Worst Grade 5 Related AE	0	0	NE	0.00 (-0.11, 0.06)
AE leading to dose reduction	31 (49%)	5 (16%)	**3.05 (1.43, 7.16)**	**0.33 (0.13, 0.49)**
AE leading to dose hold	52 (83%)	13 (42%)	**1.97 (1.36, 3.16)**	**0.41 (0.20, 0.59)**
AE leading to dose modification (reduction or hold)	56 (89%)	16 (52%)	**1.72 (1.28, 2.57)**	**0.37 (0.18, 0.56)**
AE leading to treatment discontinuation	12 (19%)	3 (9.7%)	1.97 (0.66, 6.24)	0.09 (-0.08, 0.23)
Related AE leading to treatment discontinuation	9 (14%)	1 (3.2%)	4.43 (0.79, 26.63)	0.11 (-0.03, 0.23)

Source: Table 2-30, pp 97 & 98 of the submission

AE: adverse event; CBZ: cabozantinib; CRF: Case report form; NE: not evaluable; PBO: placebo; pNET: pancreatic neuroendocrine tumour; RD: risk difference; RR: relative risk; SAE: serious adverse event.

Note: Patients counted only once within each category but may be counted in multiple categories.

RR and RD calculated during the evaluation using StatsDirect version 3.3.6, using random effects.

[a] One death occurred due to tumour (per the patient status CRF) during the safety reporting window but was not entered as a Grade 5 AE.

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

Table 11: Adverse event overview in CABINET (epNET; Safety population)

	CBZ only (n=132)	PBO (n=67)	RR	RD
AE	132 (100%)	67 (100%)	NE	0.00 (-0.03, 0.05)
Related AE	130 (98%)	56 (84%)	**1.18 (1.08, 1.35)**	**0.15 (0.07, 0.26)**
SAE	58 (44%)	27 (40%)	1.09 (0.78, 1.57)	0.04 (-0.11, 0.18)
Related SAE	38 (29%)	14 (21%)	1.38 (0.82, 2.38)	0.08 (-0.05, 0.20)
Worst Grade 3 or 4 AE	89 (67%)	26 (39%)	**1.74 (1.29, 2.45)**	**0.29 (0.14, 0.42**)
Worst Grade 3 or 4 Related AE	78 (59%)	18 (27%)	**2.20 (1.49, 3.41**)	**0.32 (0.18, 0.45)**
Worst Grade 4 AE	9 (6.8%)	1 (1.5%)	4.57 (0.78, 27.69)	0.05 (-0.02, 0.11)
Worst Grade 4 Related AE	8 (6.1%)	1 (1.5%)	4.06 (0.69, 24.83)	0.05 (-0.02, 0.10)
Worst Grade 5 AE	9 (6.8%)	5 (7.5%)	0.91 (0.34, 2.53)	-0.01 (-0.10, 0.07)
Worst Grade 5 Related AE	4 (3.0%)	1 (1.5%)	2.03 (0.31, 13.41)	0.02 (-0.05, 0.06)
AE leading to dose reduction	50 (38%)	5 (7.5%)	**5.08 (2.25, 12.02)**	**0.30 (0.19, 0.40)**
AE leading to dose hold	106 (80%)	25 (37%)	**2.15 (1.60, 3.03)**	**0.43 (0.29, 0.56)**
AE leading to dose modification (reduction or hold)	113 (86%)	28 (42%)	**2.05 (1.57, 2.80)**	**0.44 (0.30, 0.56)**
AE leading to treatment discontinuation	36 (27%)	13 (19%)	1.41 (0.82, 2.49)	0.08 (-0.05, 0.19)
Related AE leading to treatment discontinuation	34 (26%)	9 (13%)	**1.92 (1.01, 3.77)**	0.12 (0.00, 0.23)

Source: Table 2-45, pp 113 & 114 of the submission

AE: adverse event; CBZ: cabozantinib; CRF: Case report form; epNET: extra-pancreatic neuroendocrine tumour; NE: not evaluable; PBO: placebo; pNET: pancreatic neuroendocrine tumour; RD: risk difference; RR: relative risk; SAE: serious adverse event.

Note: Patients counted only once within each category but may be counted in multiple categories.

RR and RD calculated during the evaluation using StatsDirect version 3.3.6, using random effects.

Values in bold indicate significance (CI did not include 1 or 0 for RR and RD respectively).

6.39 Treatment-related AEs from CABINET were used in the submission's economic model. It was noted that:

- In the pNET cohort: AEs were considered by the investigator as related to study drug for 98% of patients in the cabozantinib arm and 84% of patients in the placebo arm. The most frequently reported treatment-related AEs (> 50% of patients in either treatment arm) were fatigue (75% cabozantinib, 39% placebo), alanine aminotransferase (ALT) increased (63% vs 26%), aspartate aminotransferase (AST) increased (63% vs 26%), diarrhea (59% vs 9.7%), and hypertension (54% vs 23%); and
- In the epNET cohort: AEs were considered by the investigator as related to study drug for 98% of patients in the cabozantinib arm and 84% of patients in the placebo arm. The most frequently reported treatment-related AEs (> 50% of patients in either treatment arm) were AST increased (65% cabozantinib, 18% placebo), fatigue (61% vs 43%), ALT increased (58% vs 15%), diarrhea (55% vs 30%), and hypertension (52% vs 21%).

The relative risk and risk differences calculated during the evaluation indicate that compared to placebo patients, patients receiving cabozantinib were significantly more likely to experience the abovementioned treatment-related AEs.

6.40 For both cohorts, the most frequently reported AEs and the most frequently reported treatment-related AEs noted above were all solicited events (considered "expected" per protocol and solicited at baseline and for each cycle of the treatment). The submission concluded that there were no new safety findings from CABINET (across both the pNET and epNET cohorts) for cabozantinib, which was in line with the CSR.

Indirect treatment comparison (third line pNET)

6.41 The following ITC of AEs from CABINET, A618-1111 and RADIANT-3 was presented by the submission (Table 12). As with efficacy outcomes, these were presented strictly for completeness. AEs were not considered in the CMA in the submission.

Table 12: Summary of ITCs on adverse events in the included trials (pNET; Safety Population)

Trial ID	Comparison	Active trt n/N (%)	PBO n /N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
At least one AE						
CABINET	CBZ vs PBO	63/63 (100)	31/31 (100)	2.0 (0.04, 104) [a]	1.0 (1.0, 1.0)	0% (-11.0%, 5.7%)
A618-1111	SUN vs PBO	82/83 (99)	78/82 (95)	4.2 (0.5, 38.5)	1.04 (0.98, 1.10)	3.7% (-1.5%, 8.9%)
RADIANT-3	EVE vs PBO	202/204 (99)	198/203 (98)	2.6 (0.5, 13.3)	1.02 (0.99, 1.04)	1.5% (-1.0%, 4.0%)
ITC	CBZ vs SUN			0.48 (0.01, 42.51)	0.96 (0.91, 1.02)	-3.7% (-13.54%, 6.14%)
	CBZ vs EVE			0.77 (0.01, 54.48)	0.98 (0.96, 1)	-1.5% (-10.22%, 7.22%)
	EVE vs SUN			0.6 (0.0, 9.6)	0.98 (0.92, 1.04)	-2.2% (-8.0%, 3.6%)
At least one Grade 3 or 4 AE						
CABINET	CBZ vs PBO	46/63 (73)	14/31 (45)	**3.3 (1.3, 8.1)**	**1.6 (1.07, 2.46)**	**28% (7.1%, 46.5%)**
A618-1111	SUN vs PBO	41/83 (49)	36/82 (44)	1.2 (0.7, 2.3)	1.13 (0.81, 1.56)	5.5% (-9.7%, 20.7%)
RADIANT-3	EVE vs PBO	122/204 (60)	79/203 (39)	**2.3 (1.6, 3.5)**	**1.54 (1.25, 1.88)**	**20.9% (11.4%, 30.4%)**
ITC	CBZ vs SUN			2.75 (0.92, 8.19)	1.42 (0.83, 2.41)	22.5% (-2.4%, 47.4%)
	CBZ vs EVE			1.43 (0.53, 3.88)	1.04 (0.65, 1.65)	7.1% (-14.8%, 30.0%)
	EVE vs SUN			1.9 (0.9, 3.9)	1.37 (0.93, 2.01)	15.4% (-2.5%, 33.3%)
At least one serious AE						
CABINET	CBZ vs PBO	29/63 (46)	7/31 (23)	**2.9 (1.1, 7.8)**	2.04 (1.01, 4.12)	**22% (4.6%, 35.1%)**
A618-1111	SUN vs PBO	22/83 (27)	34/82 (42)	0.5 (0.3, 1.0)	0.64 (0.41, 0.99)	**-15.0% (-29.2%, -0.7%)**
RADIANT-3	EVE vs PBO	82/204 (40)	50/203 (25)	**2.1 (1.3, 3.1)**	**1.63 (1.22, 2.19)**	**15.6% (6.6%, 24.5%)**
ITC	CBZ vs SUN			**5.8 (1.89, 17.83)**	**3.19 (1.39, 7.31)**	**37% (16.1%, 57.9%)**
	CBZ vs EVE			1.38 (0.47, 4.03)	1.25 (0.58, 2.68)	**6.4% (11.3%, 24.1%)**
	EVE vs SUN			**4.0 (1.8, 8.8)**	**2.55 (1.50, 4.34)**	**30.5% (13.7%, 47.4%)**
On treatment deaths (within 28/30 days of end of double-blind treatment)						
CABINET	CBZ vs PBO	1/63 (2)	0/31 (0)	1.5 (0.06, 38.2)	1.50 (0.06, 35.80)	1% (-10.1%, 7.5%)
A618-1111	SUN vs PBO	5/83 (6)	9/82 (11)	0.5 (0.2, 1.6)	0.55 (0.19, 1.57)	-5.0% (-13.4%, 3.5%)
RADIANT-3	EVE vs PBO	12/204 (6)	4/203 (2)	3.1 (1.0, 9.8)	2.99 (0.98, 9.10)	3.9% (0.2%, 7.7%)
ITC	CBZ vs SUN			3.0 (0.1, 89.13)	2.73 (0.09, 78.96)	6% (-6.2%, 18.2%)
	CBZ vs EVE			0.48 (0.02, 14.85)	0.5 (0.02, 14.8)	-2.9% (-12.5%, 6.7%)
	EVE vs SUN			**6.0 (1.2, 30.1)**	**5.44 (1.18, 25.15)**	8.9% (-0.4%, 18.1%)

Source: Table 2-56, p125 of the submission.
CBZ: cabozantinib; EVE: everolimus; HR: hazard ratio; ITC: indirect treatment comparison; ITT: intent-to-treat; NE: not estimable; NR: not reported; OR: odds ratio; OS: overall survival; PBO: placebo; RD: risk difference; RR: relative risk; SUN: sunitinib
Values in bold indicate significance (CI did not include 1 for OR or RR, or 0 for RD).
[a] Unable to be verified during the evaluation; this was 'excluded' on StatsDirect version 3.3.6, using random effects.

Unanchored indirect comparison (third line epNET)

6.42 The submission presented a table summarising safety information from the non-randomised chemotherapy studies, and a summary of typical adverse effects from CAPTEM and modified FOLFOX treatment (sourced from eviQ). These were not reproduced herein given the safety profile of chemotherapy is generally well established. Safety outcomes for cabozantinib and chemotherapy were presented separately, and a comparative safety analysis was not performed by the submission.

Benefits/harms

6.43 A summary of the comparative benefits and harms for cabozantinib versus BSC (represented by placebo) can be found in Table 5, Table 10 and Table 11.

6.44 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with cabozantinib in comparison with placebo (pNET) in the fourth line setting:

- Approximately 47 additional patients will remain progression-free (as assessed by BICR and by IA) after 6 months, however, there would be no difference in overall survival;
- Approximately 24 more patients will experience SAE(s); and
- Approximately 30 more patients will experience related SAE(s);

6.45 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with cabozantinib in comparison with placebo (epNET) in the fourth line setting:

- Approximately 35 additional patients will remain progression-free (as assessed by BICR and by IA) after 6 months, however, there would be no difference in overall survival;
- Approximately 30 or 22 additional patients will remain progression-free (as assessed by BICR or IA respectively) after 12 months, however, there would be no difference in overall survival;
- Approximately 29 more patients will experience worst grade 3 or 4 AE(s); and
- Approximately 32 more patients will experience worst grade 3 or 4 related AE(s).

6.46 A benefits and harms table was not presented for the third-line setting as the submission made a claim of non-inferiority.

Clinical claim

Third line pNET (versus sunitinib and everolimus)

6.47 For the treatment of patients with pNET in the third line setting, the submission described cabozantinib as having comparable effectiveness to sunitinib or everolimus. The ESC considered this claim was not adequately supported as the indirect comparisons (i.e. the unanchored, unadjusted "side by side" comparison, and the Bucher ITC) were difficult to interpret due to transitivity issues (although the ESC acknowledged that the submission presented the Bucher ITC "strictly for completeness"). Further, the majority of pNET patients enrolled in CABINET had previously received everolimus or sunitinib, which would reflect a later line of treatment than the proposed population. As such, the applicability of results from CABINET to the proposed third line setting may be limited.

6.48 The evaluation noted the transitivity issues with the indirect comparison, but considered that, the claim of comparable effectiveness may be biologically plausible given cabozantinib and sunitinib are both TKIs which are superior in terms of PFS to placebo, as demonstrated in CABINET and A618-1111, respectively (though the OS benefit for cabozantinib in CABINET was less convincing than for sunitinib in A618-1111, with or without adjustment for treatment switching).

6.49 The ESC considered that the clinical claim that cabozantinib has a different but manageable safety profile compared to sunitinib and everolimus was uncertain given the transitivity issues between the trials.

Third line epNET (versus chemotherapy)

6.50 The ESC considered the clinical claim that cabozantinib is comparable in terms of effectiveness versus chemotherapy (TEM-based and oxaliplatin-based regimens) was not adequately supported. The ESC noted that the PSCR acknowledged that the approach was 'pragmatic' due to poor study design, however the ESC considered that:

- Comparisons were difficult given the limited and different reporting of patient characteristics, treatment details and results between the included studies;
- The majority of epNET patients enrolled in CABINET had previously received everolimus, which would reflect a later line of treatment than the proposed population. As such, the applicability of results from CABINET to the proposed third line setting may be limited; and
- Given the included chemotherapy studies consisted entirely of retrospective chart reviews, the comparison was prone to a high risk of bias.

6.51 The submission described cabozantinib as having a different but manageable safety profile compared to chemotherapy. The ESC considered this was uncertain, noting that a comparative safety analysis was not presented in the submission.

Fourth line pNET (versus BSC)

6.52 For the treatment of patients with pNET at the fourth line setting, the submission described cabozantinib as superior in terms of effectiveness compared with BSC (represented by placebo in the CABINET trial). The ESC considered this claim may be reasonable and was adequately supported by the results of the CABINET trial, which reported a statistically significant PFS benefit in favour of cabozantinib (PFS by BICR HR=0.23; 95% CI: 0.12, 0.42; PFS by IA HR=0.29; 95% CI: 0.16, 0.52).

6.53 The evaluation noted the following uncertainties with the clinical claim:

- Compared to BSC, cabozantinib was not associated with an OS benefit (HR= 0.95; 95% CI: 0.45, 2.00) in the ITT analysis or after adjusting for treatment switching (IPCW HR= 0.74; 95% CI: 0.36, 1.52); and
- The evaluation noted that, while a significant ORR (by BICR) treatment difference was reported for cabozantinib vs placebo (18.8%; 95% CI: 9.2%, 28.3%; p=0.0115), when assessed by IA, the observed ORR for the cabozantinib arm of CABINET was reduced (from 18.8% to 7.8%) and the resultant treatment difference did not reach statistical significance (7.8%; 95% CI: 1.2%, 14.4%; p=0.1218). However, the ESC considered PFS to be more clinically meaningful than ORR, and noted that PFS was the primary outcome of the CABINET trial.

6.54 For the treatment of patients with pNET at the fourth line setting, the submission described cabozantinib as inferior (but with a manageable safety profile) in terms of safety compared to BSC. The evaluation and the ESC considered this was reasonable and supported by the evidence presented in the submission. There were no new safety findings from CABINET for cabozantinib.

Fourth line epNET (versus BSC)

6.55 For the treatment of patients with epNET at the fourth line setting, the submission described cabozantinib as superior in terms of effectiveness compared with BSC. The ESC considered this claim may be reasonable, noting that a statistically significant PFS benefit was observed in CABINET (PFS by BICR HR= 0.38; 95% CI: 0.25, 0.58; PFS by IA HR=0.41; 95% CI: 0.28, 0.60). The ESC noted that cabozantinib was not associated with an OS benefit (HR=0.86; 95% CI: 0.56, 1.31) compared to BSC in the ITT analysis or after adjusting for treatment switching (IPCW HR= 0.65; 95% CI: 0.39, 1.07). While the ORR treatment difference for cabozantinib vs placebo in the epNET cohort (by BICR) was not significant (5.2%: 95% CI: 1.5%, 9.0%; p-value= 0.0524), the ESC noted that PFS was the primary outcome of the trial and was likely to be more clinically meaningful than ORR.

6.56 For the treatment of patients with epNET at the fourth line setting, the submission described cabozantinib as inferior (but with a manageable safety profile) in terms of safety compared to BSC. The evaluation and the ESC considered this was reasonable and supported by the evidence presented in the submission.

Overall considerations on the clinical claims

6.57 The ESC considered that, overall, cabozantinib could provide an alternative treatment option in a relatively rare indication. The ESC considered the issues with the clinical claim were unlikely to be resolved with further data or analyses.

6.58 The PBAC considered that a claim of non-inferior comparative effectiveness in third line (versus sunitinib and everolimus in pNET, and chemotherapy in epNET) was clinically plausible notwithstanding the: limited applicability of the CABINET trial to the third line setting; transitivity issues; and, in the epNET setting, the poor quality of the comparator trials.

6.59 The PBAC considered the claim that cabozantinib has superior comparative effectiveness in fourth line epNET and pNET (versus BSC) was reasonable.

6.60 The PBAC considered that the claim of a different but manageable safety profile in the third line setting (versus sunitinib and everolimus in pNET, and chemotherapy in epNET) was not well-justified (e.g. given transitivity issues) but that a claim of non-inferior safety was likely reasonable

6.61 The PBAC considered that cabozantinib was associated with inferior safety versus BSC in fourth line epNET and pNET, noting there were no new safety findings for cabozantinib in the CABINET trial.

Economic analysis

6.62 The submission conducted two types of economic evaluations:

- Cost utility analyses (CUAs), comprising modelled evaluations based on direct evidence from the pivotal CABINET trial, in the fourth line setting, where the submission made a claim of superior efficacy versus BSC for both the pNET and epNET populations; and
- CMAs in the third line setting, where the submission made a claim of comparable efficacy between cabozantinib versus sunitinib (for third line pNET), and versus chemotherapy (for third line epNET).

6.63 The ESC considered that overall, the clinical data did not suggest that a substantial price premium versus sunitinib, everolimus or chemotherapy would be warranted. The pre-PBAC response stated that a weighted price derived across the CMA and CUAs provides a basis for listing, as "a simple CMA compared to existing treatments does not reflect expected clinical use nor support a viable price for PBS listing".

Weighted price

6.64 The submission proposed a single weighted DPMQ for cabozantinib across the epNET and pNET settings. The price was derived from separate CUAs and CMAs for the defined patient groups, with the price weighted by expected utilisation across groups in pNET and epNET (see Table 13), noting the requested DPMQ was reduced in the pre-PBAC response to $[redacted] (see Table 14). The pre-PBAC response stated that "There are limited treatments available in Australia for patients with epNETs, and it may be more appropriate to consider that the split between the CMA price and CUA price reflects a mixed comparator rather than a strict line of treatment".

Table 13: Calculation of cost-effective price of cabozantinib (pNET and epNET; presented by the submission)

	% patients [a]	CMA vs SUN/EVE (pNET) or chemo (epNET) in 3L [b]		CEA vs BSC in 4L		ICER $/QALY	Indication DPMQ ($)	Weighted DPMQ ($)
		DPMQ ($)	%	DPMQ ($)	%			
pNET	14%	$1,835.67	26.3%	[redacted]	73.7%	[redacted][1]	[redacted]	
epNET	86%	$925.90	36.5%		63.5%	[redacted][2]		

Source: Table 3-2, p142 of the submission. 3L: third line; 4L: fourth line; BSC: best supportive care; CE: cost effective; CEA: cost effectiveness analysis; CMA: cost minimisation approach; DPMQ: dispensed price for maximum quantity; epNET: extra-pancreatic neuroendocrine tumour; EVE: everolimus; ICER: incremental cost-effectiveness ratio; pNET: pancreatic neuroendocrine tumour; QALY: quality-adjusted life year; SUN: sunitinib

[a] The proportion of pNET vs. epNET based on AIHW epidemiological data (consistent with data used in the submission's financial model)

[b] The proportion of patients enrolled in CABINET who accessed prior therapies. This may not be appropriate; the submission did not provide any reasonings for using these proportions.

26.3% refers to the % of patients in pNET cohort who received prior sunitinib, based on Table 33 of the CSR. It was unclear why sunitinib was used, instead of everolimus, noting 80% of patients in the pNET cohort had received prior everolimus.

36.5% refers to the % of patients in epNET cohort who received prior cytotoxic chemotherapy regimens, based on Table 16 of the CSR. It was noted that 69% of patients in the pNET cohort had received prior everolimus.

The redacted values correspond to the following ranges:

[1] *$45,000 to < $55,000*

[2] *$55,000 to < $75,000*

6.65 The weighted DPMQs were updated during the evaluation (see Table 14):

- To reflect the price reduction of sunitinib that occurred since the submission (see Table 23); and
- Based on an assumption of the same duration of PFS (the proxy for treatment) for cabozantinib and chemotherapy (CAPTEM and FOLFOX) for third line epNET given the claim of non-inferiority (see paragraph 6.106).

The ESC and PBAC considered these changes were appropriate.

6.66 The evaluation and the ESC noted the following points regarding the submission's requested weighted price:

- The price derived from the CUAs (versus BSC) was substantially higher than from the CMAs;
- Given the weighted DPMQ was calculated based on estimated utilisation across groups, if the proportion of use across the four requested populations differs in clinical practice, then the weighted DPMQ would be inaccurate.
- The proportion of patients in the third-line settings may be underestimated, which would overestimate the weighted price (refer to paragraph 6.68).
- The submission's reported incremental cost-effectiveness ratio (ICER) for fourth line epNET $55,000 to < $75,000 /QALY) was considerably (39%) higher than the reported ICER for the fourth line pNET population ($45,000 to < $55,000/QALY), but the requested price remained the same ($[redacted]). The PSCR stated that the reported ICER for patients with epNET is within the range previously accepted by PBAC for late-stage oncology indications with high clinical need. However, the ESC considered that it would be appropriate for the ICERs to be the same for patients with pNET and epNET. Thus, the pre-PBAC response proposed the same ICER in both settings based on the higher of the two ICERs (i.e. $55,000 to < $75,000 /QALY for both pNET and epNET, refer to Table 14) but with different indication-specific prices in each of the settings (i.e. DPMQs of $[redacted] in fourth line pNET and $[redacted] in fourth line epNET). However, the PBAC considered an ICER of no higher than $55,000 to < $75,000 /QALY would be reasonable in epNET. Further, the PBAC considered that the price required to achieve this ICER should also be applied to the pNET setting (i.e. the indication-specific price should be the same in both pNET and epNET in the fourth line setting), as outlined in paragraph 7.15 (based on the revised base case specified in paragraph 7.14). This is included in Table 14 as 'PBAC step 1'.

Table 14: Sensitivity analyses around the weighted price of cabozantinib and the PBAC recommended scenario

	% patients [a]	CMA vs SUN/EVE (pNET) or chemo (epNET) in 3L [b]		CEA vs BSC in 4L		ICER $/QALY	Indication DPMQ ($)	Weighted DPMQ ($)
		DPMQ	%	DPMQ ($)	%			
Submission base case								
pNET	14%	$1,835.67	26.3%	[redacted]	73.7%	[redacted][1]	[redacted]	
epNET	86%	$925.90	36.5%		63.5%	[redacted][2]		
#A Updates during evaluation: (a) sunitinib price updated; and (b) same duration of PFS (the proxy for treatment) assumed for cabozantinib and chemotherapy for third line epNET								
pNET	14%	$1,627.37 [c]	26.3%	[redacted]	73.7%	[redacted][1]	[redacted]	
epNET	86%	$785.16 [d]	36.5%		63.5%	[redacted][2]		
Evaluation Sensitivity analysis 1: weighting between 3L and 4L as per financial estimates								
pNET	24% [e]	$1,627.37 [c]	54.1%	[redacted]	45.9%	[redacted][1]	[redacted]	
epNET	76% [e]	$785.16 [d]	59.6%		40.4%	[redacted][2]		
Evaluation Sensitivity analysis 2: proportion of pNET and epNET as per the values reported in Wyld 2019								
pNET	11% [f]	$1,627.37 [c]	54.1%[g]	[redacted]	45.9%	[redacted][1]	[redacted]	
epNET	89% [f]	$785.16 [d]	59.6%[g]		40.4%	[redacted][2]		
Pre-PBAC response revised weighted price								
pNET	14%	$1,627	26.3%	[redacted]	73.7%	[redacted][2]	[redacted]	
epNET	86%	$812 [h]	25.0% [i]		75.0%	[redacted][2]		
Derivation of the scenario recommended by the PBAC (stepped approach)								
PBAC step 1: Scenario #A plus CUA base case respecified per paragraph 7.14 with an ICER of $75,000 per QALY in epNET, with the required price flowed on to pNET as outlined in paragraph 7.15								
pNET	14%	$1,627	26.3%	[redacted][j]	73.7%	[redacted][2]	[redacted]	
epNET	86%	$785 [h]	36.5%	[j]	63.5%	[2]		
PBAC step 2: Step 1 plus apply CAPTEM : FOLFOX ratio of 60% : 40% as outlined in paragraph 7.16								
pNET	14%	$1,627	26.3%	[redacted][j]	73.7%	[redacted][2]	[redacted]	
epNET	86%	$687	36.5%	[j]	63.5%	[2]		
PBAC step 3: Step 2 plus apply 3L to 4L ratio of [redacted]% to [redacted]% as outlined in paragraph 7.12								
pNET	14%	$1,627	40%	[redacted][j]	60%	[redacted][2]	[redacted]	
epNET	86%	$687	40%	[j]	60%	[2]		
<u>Scenario recommended by the PBAC</u> **PBAC step 4: Step 3 plus adjust pNET to epNET ratio to align more closely with financial estimates inputs (i.e. take into account differential proportions with Stage IV disease in pNET and epNET) per paragraph 7.13**								
pNET	19% [k]	$1,627	40%	[redacted][j]	60%	[redacted][2]	[redacted]	
epNET	81% [k]	$687	40%	[j]	60%	[2]		

Source: Table 3-2, p142 of the submission. Constructed during the evaluation and preparation of the PBAC Minutes

3L: third line; 4L: fourth line; BSC: best supportive care; CE: cost effective; CEA: cost effectiveness analysis; CMA: cost minimisation approach; DPMQ: dispensed price for maximum quantity; epNET: extra-pancreatic neuroendocrine tumour; EVE: everolimus; ICER: incremental cost-effectiveness ratio; pNET: pancreatic neuroendocrine tumour; QALY: quality-adjusted life year; SUN: sunitinib

[a] Base case: The proportion of pNET vs. epNET was based on AIHW epidemiological data (consistent with data used in the submission's financial model)

[b] Base case: The proportion of patients enrolled in CABINET who accessed specific prior therapies. For pNET: 26.3% refers to the % of patients in pNET cohort who received prior sunitinib, based on Table 33 of the CSR. For epNET: 36.5% refers to the % of patients in epNET cohort who received prior cytotoxic chemotherapy regimens, based on Table 16 of the CSR. It was noted that 69% of patients in the pNET cohort had received prior everolimus.

[c] Price updated during the evaluation to reflect price reduction of sunitinib

[d] Price updated during the evaluation assuming equal duration of treatment between cabozantinib and chemotherapy (as per claim of non-inferiority

[e] The proportion of pNET vs. epNET, based on the total number of scripts over 6 years in the submission's financial model; i.e. 7,487/31,154 and 23,667/31,154 for pNET and epNET respectively.
[f] The proportion of pNET vs. epNET based on ratio of scripts from a sensitivity analysis of the financial estimates using values from Wyld 2019 instead of Bodei 2017; based on the total number of scripts over 6 years i.e. 3,113/29,012 and 25,899/29,012 for pNET and epNET respectively.
[g] The proportion of patients receiving 3L vs 4L for pNET and epNET, based on the total number of scripts over 6 years in the financial model using Wyld 2019; i.e. 1,685/3,113 and 1,428/3,113 pNET patients receiving 3L and 4L respectively, and 15,433/25,899 and 10,466/25,899 epNET patients receiving 3L and 4L respectively.
[h] The pre-PBAC response updated the duration of therapy with FOLFOX to be consistent with the duration for cabozantinib, but did not update the duration for CAPTEM. The PBAC recommended that the CMA should assume the same treatment durations for chemotherapy (i.e. both CAPTEM and FOLFOX) and cabozantinib.
[i] The pre-PBAC response stated 'Clinicians advise that only a small proportion of pre-treated epNETs patients currently receive chemotherapy, which is generally considered ineffective in this setting. An estimate of 25% use of chemotherapy in pre-treated epNETs is applied in the revised base case'. The PBAC did not accept this change.
[j] DPMQ required for an ICER of $55,000 to < $75,000 per QALY in 4L epNETs (based on pre-PBAC response revised economic model, but with Kaplan-Meier data applied for 24 months, rather than 12 months), then the price required to achieve this ICER was applied to the pNET setting (refer to paragraphs 7.14 and 7.15)
[k] The proportion of patients with Stage IV disease was applied to the AIHW epidemiological data for the proportion of patients with pNET versus. epNET (i.e. as outlined in Table 28, White 2022 estimated that 37.16% and 25.72% of patients with pNET and epNET have Stage IV disease, respectively. This resulted in a ratio of 19.4% and 80.6% relative weighting between pNET and epNET, respectively).
The redacted values correspond to the following ranges:
[1] *$45,000 to < $55,000*
[2] *$55,000 to < $75,000*

6.67 Two sensitivity analyses were conducted during evaluation (refer to Table 14) testing alternative assumptions for the weightings between: third- versus fourth-line (refer to paragraphs 6.68 and 6.69); and pNET versus epNET (paragraph 6.70).

6.68 The proportion of patients in fourth line was based on the proportion of patients enrolled in CABINET who accessed prior sunitinib treatment for the pNET population and prior cytotoxic chemotherapy regimens for the epNET population. For pNET, it was unclear why this was based on prior sunitinib treatment only, given 80% of patients in CABINET had received prior everolimus. The ESC considered that CABINET may not be a reliable basis for informing the proportion of patients in the PBS population who would use cabozantinib in third line versus fourth line given the trial enrolled later-line patients than would be eligible in the PBS restriction. In particular, the evaluation considered that incident patients may be more likely to access cabozantinib in the third-line epNET setting given cabozantinib would be the only PKI available for epNET (refer to paragraph 6.116). The weighting in pNET was also contingent on whether sequential use of cabozantinib, sunitinib and everolimus is allowed (see paragraph 3.5). Overall, the ESC and PBAC considered it did not seem plausible for there to be nearly three time more patients in the fourth line setting versus the third line setting in pNET (73.7% versus 26.3%).

6.69 Further, the proportion of use in third line was lower than in the financial estimates which was based on US hospital databases and uptake assumptions. As such, a sensitivity analysis using the financial model's estimated proportion of utilisation (based on the number of scripts) as well as the CMA prices calculated during the evaluation was conducted (see Table 14), which reduced the weighted DPMQ by 27%. The ESC considered that while this may be more reasonable than the weightings used in the submission; overall the ESC considered that utilisation in third line versus fourth

line was difficult to predict and any sensitivity analyses should be interpreted with caution. The pre-PBAC response stated that "it would be inappropriate for the proportions from the financial estimates to be applied in the weighted price calculations" since "the proportions derived from the financial estimates are based on scripts, and therefore duration of treatment, however, the cost-effective prices used in the weighted price calculation already account for this". The PBAC agreed with the ESC that utilisation in third line versus fourth line would be difficult to predict. Overall, in the absence of reliable data, the PBAC considered that the ratio of use of cabozantinib should be 40% use in third line versus 60% use in fourth line (refer to paragraph 7.11).

6.70 The proportion of pNET and epNET patients (in NETs) applied in the submission's financial estimates (14% and 86% respectively) differed to values reported in Wyld 2019, a study of epidemiological trends of NETs in Queensland, Australia (referred to by the submission in Section 1). The proportions from Wyld 2019 (250/4115, 5.66% pNET and 4165/4115, 94.34% epNET, excluding those with unknown primary tumour site, and updated for uptake assumptions) were tested in a sensitivity analysis during evaluation (see Table 14). The PSCR stated that Wyld 2019 was based on all patients with NETs across a 30-year period with the paper stating the prevalence of cancers by primary site had shifted over the course of the 30-year observation period.

6.71 The PBAC noted the proportion of pNET and epNET patients (in NETs) applied in the submission's financial estimates (14% and 86% respectively) was based on AIHW data, but that the financial estimates subsequently applied the proportion of patients with stage IV disease (based on White 2022), which differed between pNET and epNET. As outlined it the footnotes to Table 14, once these proportions were applied, the relative weighting of pNET to epNET changed to 19% to 81%, respectively. The PBAC considered these should be applied to the calculation of the weighted price, to more closely align with the inputs for the financial estimates.

Cost utility analysis

6.72 The submission presented a stepped economic evaluation based on the CABINET trial (cabozantinib vs BSC (represented by placebo in CABINET)) to support the listing of cabozantinib in the fourth line setting for pNET and epNET. The type of economic evaluation presented was a CUA. Separate models for pNET and epNET were provided by the submission. The method to generate results (a partitioned survival model) was similar for both models but the inputs and assumptions differed. The key components of the economic models are summarised in Table 15.

Table 15: Summary of model's structure, key inputs and rationale (pNET and epNET)

Component	Description	Justification/ evaluation comments
Treatments	Cabozantinib vs BSC (pNET and epNET)	Appropriate.
Type of analysis	Cost-utility analysis	Reasonable. Consistent with the submission's clinical claim of superior efficacy of CBZ compared to BSC for both populations, which the ESC considered were reasonably supported
Outcomes	Cost per quality-adjusted life year gained	
Patient population	pNET and epNET	
Time horizon	10 years in the model base case vs. median follow-up of: - 23.2 months (CBZ arm) and 25.2 months (PBO arm) in CABINET for pNET; and - 23.3 months (CBZ arm) and 23.0 months (PBO arm) in CABINET for epNET. Adjusted to 7.5 years in the pre-PBAC response.	The evaluation and the ESC considered that a 10year time horizon was likely optimistic and uncertain given the length of follow-up in the CABINET trial as well as the proposed line of therapy. The PBAC had previously considered that a 10-year time horizon for sunitinib in pNET (which is used in an earlier line of treatment compared to the submission's proposed model) was overestimated in a progressive metastatic disease and a high progression rate (p5, sunitinib PSD, July 2012 PBAC meeting). The ESC considered that a shorter time horizon of 5 to 7 years in the fourth line setting was likely to be more appropriate.
Methods used to generate results	Partitioned survival model	Appropriate.
Health states	Three health states: - progression-free (further partitioned by a separate time to treatment discontinuation) - progressed disease - death	Appropriate.
Health related quality of life	CABINET IPD informed the value for the PF state; the decrement identified for PD from Swinburn 2012 was applied to the PF utility value obtained from CABINET to inform the value for the PD state. pNET: PF: 0.819; PD: 0.650 epNET: PF: 0.731; PD: 0.580	Compared to the PF utility values identified from published literature (range: 0.767-0.826), the PF health state for pNET (0.819) was on the higher end, while the PF health state for epNET (0.731) was observed to be lower than the reported range.
Cycle length	4 weeks	Appropriate.
Transition probabilities	Parametric extrapolation of patient-level data for PFS, OS and TTD in the CBZ arm from the pNET and epNET subpopulations in CABINET. PFS and OS for BSC was estimated using a HR approach, where a HR was applied to the extrapolated CBZ survival curve.	The evaluation and the ESC considered that the application of the HR approach to estimate overall survival on the BSC arm of the model may not be reasonable given an OS benefit was not observed between CBZ and BSC, for both the pNET and epNET cohorts.
Software package	Excel	Reasonable.

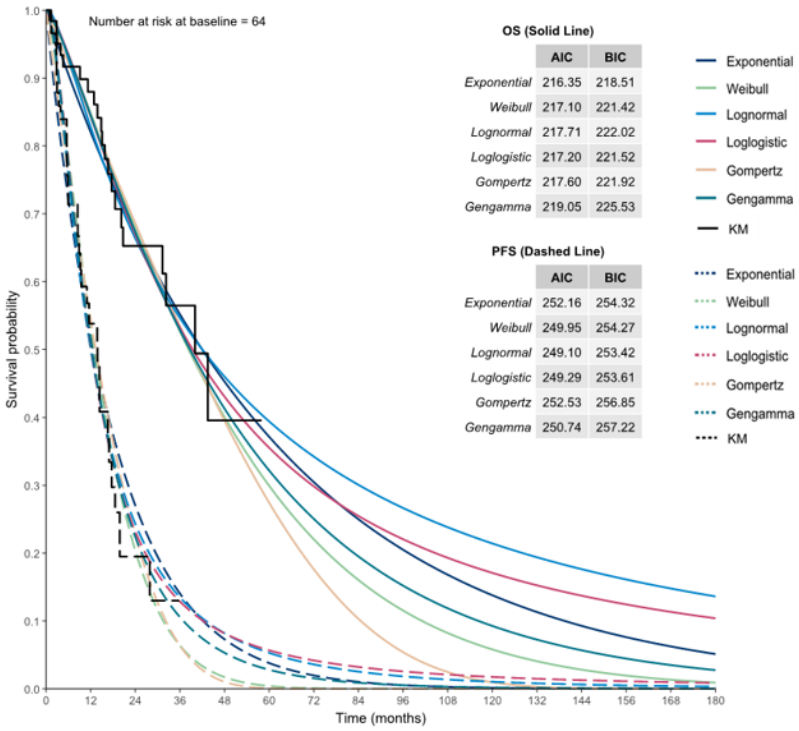
Source: Table 3-12, p159 of the submission.

BSC: best supportive care; CBZ: cabozantinib; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; IPD: individual patient data; OS: overall survival; PBO: placebo; PD: progressed disease; PF: progression-free; pNET: pancreatic neuroendocrine tumour; TTD: time to treatment discontinuation

6.73 Extrapolation of the OS and PFS data from CABINET was required to estimate the proportion of patients in each health state across the time horizon of the model. In the base case, OS and PFS in the cabozantinib arm were extrapolated using parametric functions, while OS and PFS in the BSC arm were generated relative to survival curves applied in the cabozantinib arm using a HR approach (i.e. a HR was applied to the PFS

and OS curve for the cabozantinib arm to determine the PFS and OS for BSC, as the submission outlined that, for OS, an inspection of Schoenfeld and log cumulative hazard plots showed that there was no compelling evidence of proportional hazards violation for the epNET and pNET cohorts). The submission's economic evaluation did not use any KM survival data directly at any point in the model, and the reason for this was not explained, though KM data were applied in the pre-PBAC response model. For the pNET population, the model fit and OS and PFS extrapolations (including the associated Akaike's information criteria (AIC) and Bayesian information criteria (BIC) values are provided in Figure 9 (for the cabozantinib arm).

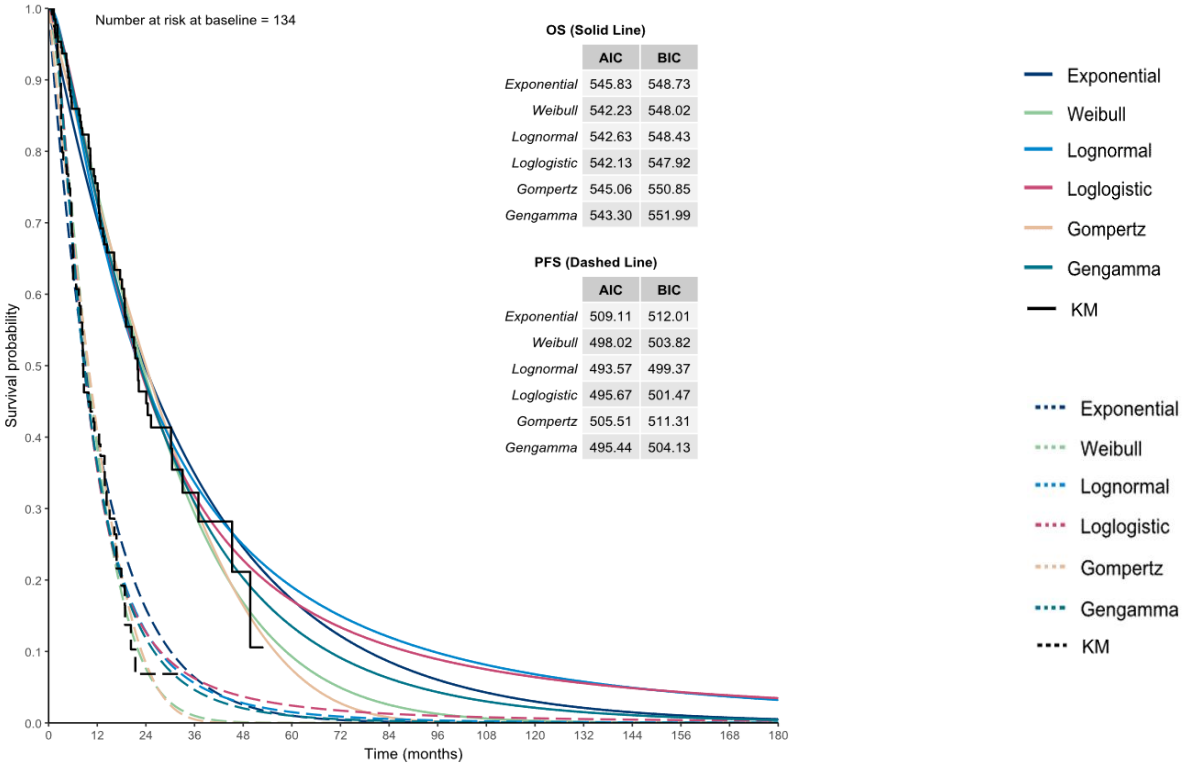
Figure 9: Parametric OS and PFS extrapolation for the cabozantinib arm (pNET cohort; ITT analysis) in the submission's economic model



Source: Figure 3-5, p179 of the submission.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intent-to-treat; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumour

6.74 For the epNET population, the model fit and OS and PFS extrapolations (including the associated AIC and BIC values) are provided in Figure 10 (for the cabozantinib arm).

Figure 10: Parametric OS and PFS extrapolation for the cabozantinib arm (epNET cohort; ITT analysis) in the submission's economic model



OS (Solid Line)

	AIC	BIC
Exponential	545.83	548.73
Weibull	542.23	548.02
Lognormal	542.63	548.43
Loglogistic	542.13	547.92
Gompertz	545.06	550.85
Gengamma	543.30	551.99

PFS (Dashed Line)

	AIC	BIC
Exponential	509.11	512.01
Weibull	498.02	503.82
Lognormal	493.57	499.37
Loglogistic	495.67	501.47
Gompertz	505.51	511.31
Gengamma	495.44	504.13

Source: Figure 3-7, p181 of the submission.
AIC: Akaike information criterion; BIC: Bayesian information criterion; epNET: extra-pancreatic neuroendocrine; ITT: intent-to-treat; KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival

6.75 The time to treatment discontinuation (TTD) curves in pNET and epNET, which were used to estimate the amount of time patients remained on treatment with cabozantinib (and SSA), were also extrapolated from CABINET. As with PFS and OS, a HR was applied to the TTD curve for cabozantinib to determine the TTD for BSC. As HRs for TTD were not reported in CABINET, the submission fitted Cox proportional hazards models to estimate the relative treatment effect of cabozantinib versus placebo for the pNET and epNET cohorts without any distributional assumptions (see Table 16).

6.76 The distributions applied in the model base case used parametric distributions identified using the best-fitting models typically determined by the lowest value AIC and BIC. A summary of base case inputs for time to event data for the pNET and epNET populations are presented in Table 16. The HR estimates applied in the base case are also presented in the table below.

Table 16: Summary of time to event data applied in the model's base case

	CBZ: parametric extrapolation	BSC: HR applied to CBZ
pNET		
PFS	Lognormal (best-fitting model)	HR=0.23; 95%CI: 0.12, 0.42 (trial-based ITT HR for PFS by BICR)
OS	Exponential (best-fitting model)	HR=0.74; 95%CI: 0.36, 1.52 (IPCW HR untruncated weights) [a]
TTD	Exponential (best-fitting model)	HR=0.36; 95%CI: 0.22, 0.60 [b]
epNET		
PFS	Lognormal (best-fitting model)	HR=0.38; 95%CI: 0.25, 0.58 (trial-based ITT HR for PFS by BICR)
OS	Loglogistic (best-fitting model)	HR=0.65; 95%CI: 0.39, 1.07 (IPCW HR untruncated weights) [a]
TTD	Exponential (best-fitting model)	HR=0.57; 95%CI: 0.41, 0.79 [b]

Source: Table 3-23, p185 of the submission.

BICR = blinded independent central review; CI = confidence interval epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; IPCW: ITT: intent-to-treat; OS: overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; TTD: time to treatment discontinuation

[a] Adjusted for treatment switching using the IPCW approach

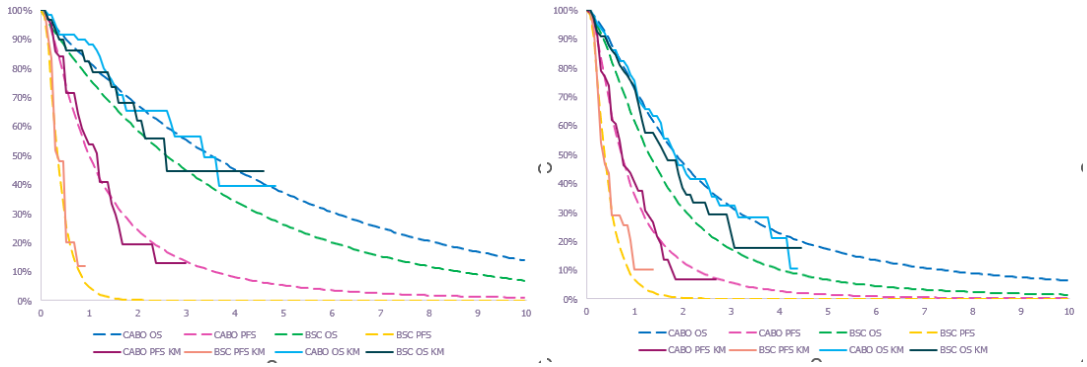
[b] As no results for TTD were reported in the CSR, Cox proportional hazards models were fitted by the submission (p43, Attachment 7 to the submission) to estimate the relative treatment effect of cabozantinib versus placebo for the pNET and epNET cohorts without any distributional assumptions. Stratified HR results are displayed; stratification factors per OPEN were used (pNETs: concomitant SSA use and prior sunitinib use; epNETs: concomitant SSA use and primary site [midgut/unknown vs non-midgut GI/lung/other]).

6.77 Overall, the evaluation and the ESC considered that the submission's approach to modelling OS, PFS and TTD likely favoured cabozantinib as:

- The model assumed an OS benefit associated with cabozantinib, by applying the treatment-adjusted IPCW HR to the extrapolated cabozantinib survival estimates. However, the clinical evidence presented by the submission suggested that cabozantinib was not associated with a statistically significant OS benefit in either the pNET (HR= 0.95; 95% CI: 0.45, 2.00) or epNET (HR=0.86; 95% CI: 0.56, 1.31) populations in the ITT analysis, even with the IPCW adjustment (pNET HR=0.74; 95% CI: 0.36, 1.52; epNET HR=0.65; 95% CI: 0.39, 1.07). Therefore, the evaluation and the ESC considered that it may not be reasonable to assume a treatment difference, and the observed OS benefit was likely overestimated in the modelled evaluation (noting the economic model estimated 0.88 and 0.97 incremental life years gained in the pNET and epNET cohorts, respectively).
- The ESC considered the use of a HR to model OS for BSC relative to the cabozantinib arm (and the resultant use of a common functional form, rather than direct parametric extrapolation of both arms), and not directly modelling post-progression survival meant that the OS curves continued to separate despite patients in the BSC arm receiving more post-progression therapy (which was costed but assumed to be ineffective).
- The use of extrapolations only instead of using KM data and then switching to extrapolation at a later time point favoured cabozantinib. A sensitivity analysis conducted during the evaluation which used KM data for the first 24 months of the model increased the ICER by 19% in pNET and 6% in epNET. The ESC considered that KM data should be used for as long as the data are considered to be reliable. Overall, the ESC considered the extrapolation approach used in

the submission appeared to overestimate incremental survival gains in comparison to the trial data (Figure 11). The pre-PBAC response provided a revised economic model in which Kaplan-Meier data were applied for 12 months (approximately the mid-point between the time to crossover and the median follow-up) for OS, PFS and time on treatment. However, the PBAC considered that Kaplan-Meier data should be applied for 24 months rather than 12 months given the modelling of OS appeared optimistic (refer to paragraph 7.14).

Figure 11: Predicted and observed OS and PFS in the submission's economic model (noting): pNET (left) and epNET (right



Source: Compiled during ESC, based on the curves labelled as KM data in the submission's economic model.
Note: OS extrapolation was based on the best-fitting parametric extrapolation for the cabozantinib arm, with the IPCW HR applied for the BSC arm; the trial KM curves are depicted above (i.e. not adjusted for cross-over)

6.78 The submission claimed that patients with NETs have access to various therapies in the post-progression setting, though treatment options may be more limited at the fourth line setting. In CABINET, the proportion of patients receiving subsequent therapy ranged between 45-66% across both the pNET and epNET population, and patients randomised to the placebo arm were more likely to receive additional therapy. The cost of subsequent therapies applied in the submission's economic model is presented in Table 17. To avoid double-counting terminal care costs, an adjustment to the treatment cost was performed by assuming that patients do not receive therapies in the last 12 months of life.

Table 17: Mix of subsequent therapies applied in the models (pNET and epNET)

	Cost per cycle (incl admin)	pNET		epNET	
Treatment		**CBZ**	**BSC**	**CBZ**	**BSC**
% receiving subsequent Rx	-	51.02%	62.07%	45.05%	66.67%
SUN	-	0	0	0	0
EVE	-	0	0	0	0
PRRT (Lu-177)	$8,080.06	[redacted]%	35.29%	[redacted]%	40.63%
External beam radiation therapy	$2,281.25	[redacted]%	5.88%	[redacted]%	12.50%
CAPTEM	$276.80	[redacted]%	29.41%	[redacted]%	23.44%
FOLFOX	$1,188.84	[redacted]%	29.41%	[redacted]%	23.44%
Lanreotide	$883.67	[redacted]%	27.42%	[redacted]%	34.78%
Octreotide	$637.60	[redacted]%	27.42%	[redacted]%	34.78%
Weighted cost per cycle		$1[redacted]	$2,379.83	$[redacted]	$2,960.22
Weight cost per cycle (adjusted for no treatment during last 12 months of life) [a]		$[redacted]	$1,601.54	$[redacted]	$877.59

Source: Table 3-37, 3-39 & 3-40, pp197 & 198 of the submission.

177-Lu: 177 Lu-DOTA-octreotate; BSC: best supportive care; CAPTEM: CAPTEM: capecitabine and temozolomide; EVE: everolimus; FOLFOX: FOLFOX: leucovorin/fluorouracil/oxaliplatin; PD: progressive disease; pNET: pancreatic neuroendocrine tumour; SUN: sunitinib; CBZ : cabozantinib

Note: Percentage (excluding SSAs) add up to 100%

[a] The model assumed no subsequent treatment for the final 12 months in the PD health state. Therefore, the cost of subsequent treatments was multiplied by the proportion of time spent in PD adjusted by 12 months. This was 0.64 for the CBZ arm ($[redacted] * 0.64 = $[redacted]) and 0.67 in the BSC arm ($2,379.83 * 0.67 = $1601.54) for pNET. This was 0.44 for the CBZ arm ($[redacted] * 0.44 = $[redacted]) and 0.30 for the BSC arm ($2960.22 * 0.30 = $877.59) for epNET.

Grey shading indicates lanreotide and octreotide as concomitant therapy but included as part of subsequent therapy during the PD phase in the modelled evaluation.

6.79 The evaluation considered the submission's modelling of subsequent therapies was not reasonable as:

- The submission's assumption of different subsequent therapies led to a difference between treatment arms in subsequent treatment costs, being more pronounced in pNET (around $[redacted] per cycle more for BSC) than in epNET (around $6 per cycle more for BSC);
- The majority of subsequent treatment in the placebo arm of CABINET was to cabozantinib, which is not an option currently on the PBS and it was unreasonable to have assumed these patients would be treated with an alternative in the absence of cabozantinib. Further, the submission assumed that a large proportion of patients (35% and 41% in the pNET and epNET arms, respectively) would receive subsequent treatment with PRRT, which was included as a prior line of therapy in the submission's proposed treatment algorithm;
- In the Australian setting, patients receiving fourth line therapy (particularly BSC) may have exhausted treatment options or may not be clinically suitable for active treatment; and
- It may not be reasonable to assume a difference in the proportion of patients receiving subsequent treatment after progression between treatment arms, as

patients in both arms would have the same options available to them (albeit, as noted in the previous dot point, these options may be limited) and be in the same health state with the same HRQoL. The PSCR stated that the model assumed that patients in the BSC arm received no active anti-cancer treatment and thus may be more likely to seek further treatment than those who receive an active line of treatment at fourth line.

6.80 Therefore, the evaluation considered that the proportions of patients estimated to receive additional therapy in the model were likely overestimated compared to the Australian setting, particularly for the BSC arm, favouring cabozantinib. Additional sensitivity analyses were conducted during the evaluation, which assumed that the proportion of patients receiving additional treatment in the BSC arm was reduced to match the proportion in the cabozantinib arm, and the proportion of patients in both arms of the model receiving additional therapy was reduced and equalised. This led to a 31-37% increase to the resultant ICER for the pNET population and appeared to be a key driver of the model. This was less pronounced for the epNET population (increased the ICER by 10-12%). The ESC considered that it was not reasonable for the model to assume higher use of subsequent therapies in the BSC arm (relative to cabozantinib) while survival continues to diverge in patients with progressed disease, and that this likely biased the model in favour of cabozantinib. Overall, the ESC considered that if use of post-progression therapies is assumed to be higher for patients receiving BSC than cabozantinib, then it would be appropriate to also include the effectiveness of that treatment in the models. The pre-PBAC response's revised base case addressed this issue by assuming the same proportion of patients would use post-progression therapies in the cabozantinib and BSC arms.

6.81 Patient-level HRQoL data (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)) from CABINET were mapped by the submission to EQ-5D-3L using the response mapping algorithm proposed by Longworth 2014, as input for utility analyses to inform the cost utility analysis. These were not provided in the CSR and therefore could not be independently verified during the evaluation. However, the submission found that there was a lack of difference between estimated PF and PD utility values in their primary analysis. A comparison of baseline characteristics of these two groups in the pooled cohort (pNET and epNET combined) suggested the patients who progressed and reported a response in the PD health state were, on average, healthier than those who progressed and did not report a response whilst in the PD health state.

6.82 The submission concluded that given the extent of information available for PF, the estimates of PF utility were expected to be reliable; however, given missing data on PD patients, estimates of PD utility were likely to be overestimated. Compared to the PF utility values identified from published literature (range: 0.767-0.826), the PF health state for pNET (0.819) in CABINET was on the higher end, while the PF health state for epNET (0.731) was observed to be lower than the reported range. Therefore,

the PD utility value was estimated by applying a decrement (based on Swinburn 2012, a study of a time trade-off approach in which health states were developed based on clinician (N=6) and patient (N=5; pNET n=3 and GI-NET n=2) interviews and EQ-5D questionnaires) to the PF utility value. This decrement was based on the difference observed between PF and PD utility values reported in Swinburn 2012 (0.771-0.612=0.159, which represented a 20.62% decrease).

6.83 The application of alternative utility values from published literature (Swinburn 2012, Glover 2021 and Pavel 2017) was tested in sensitivity analyses during the evaluation. These led to an increase in the ICER ([redacted]%-[redacted]%) for the pNET population, but a decrease in the ICER ([redacted]%-[redacted]%) for the epNET population.

6.84 Half cycle correction was applied in the model. Inappropriately this was applied to drug costs. This was corrected in the pre-PBAC response's revised base case.

6.85 A summary of the key drivers of the models is provided in Table 18. Overall, the evaluation and the ESC considered that the modelled evaluation presented by the submission likely favoured cabozantinib.

Table 18: Key drivers of the models (pNET and epNET) based on the submission's model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained (pNET); $[redacted][2]/QALY gained (epNET)
Subsequent therapy	The proportion of patients receiving subsequent therapy was based on CABINET, in which patients randomised to the placebo arm were more likely to receive additional therapy. The pre-PBAC response's revised base case addressed this issue by assuming the same proportion of patients would use post-progression therapies in the cabozantinib and BSC arms.	Moderate-High, favours cabozantinib. Once the proportion of patients receiving subsequent treatment in the BSC arm was adjusted to be equal to the proportion of patients receiving additional treatment in the cabozantinib arm, the ICER increased by [redacted]% (pNET) and [redacted]% (epNET). This change was made in the pre-PBAC response's revised base case.
Modelling approach for BSC	Parametric extrapolation of patient-level data for PFS and OS in the cabozantinib arm from the pNET and epNET subpopulations in CABINET. PFS and OS for BSC was estimated using a HR approach, where a HR was applied to the extrapolated cabozantinib survival curve in the base case. Given the lack of statistical significance in OS in CABINET (with or without adjustment for treatment switching), the evaluation and the ESC considered it was likely unreasonable to have modelled any difference in OS between treatment arms (i.e. no OS benefit modelled for pNET and epNET populations).	High, favours cabozantinib. While using the ITT HR or extrapolation approach did not have a large impact on the ICER in the base case (decreased by [redacted]-[redacted]% for pNET and decreased by 1-[redacted]% for epNET), once the proportion of patients receiving subsequent treatment post progression was adjusted to be equal in both arms, the use of a less favourable OS HR (from the ITT analysis) resulted in an [redacted]% and [redacted]% increase in the ICER for pNET and epNET, respectively.
KM data	The economic evaluation did not model KM survival data directly at any point in the model, and the reason for this was not explained by the submission. The pre-PBAC response's revised base case partially addressed this issue by applying KM data for the first 12 months, however the PBAC considered KM data should be applied for the first 24 months.	Moderate, favours cabozantinib. The use of KM data to inform the first 24 months of the model was tested and found to increase the ICER by [redacted]% in pNET and [redacted]% in epNET. The ESC considered that KM data should be used to inform the model.
Utilities	Utility value reported for the PF health state (0.819) was found to be on the higher end compared to literature (range: 0.767-0.826).	Moderate, favours cabozantinib (pNET). When alternative utility values were tested, this led to increase in the ICER ranging from [redacted]-[redacted]% in the pNET population.
Time horizon	A 10-year time horizon was nominated in the base case. The pre-PBAC response's revised base case addressed this issue by applying a 7.5 year time horizon.	Moderate. The evaluation and the ESC considered a shorter time horizon of 5 to 7 years may be more reasonable given the assumption of a later line setting than sunitinib. Decreasing the time horizon to 5 years increased the ICER by [redacted]%.

Source: Constructed during the evaluation.
BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; KM: Kaplan-Meier; HR: hazard ratio; ITT: intention-to-treat; SSA: somatostatin analogue; OS: overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; QALY: quality-adjusted life year.
The redacted values correspond to the following ranges:
[1] *$45,000 to < $55,000*
[2] *$55,000 to < $75,000*

6.86 Notably, in the submission's model, applying the HR based on the ITT analysis (rather than the crossover-adjusted HR) to estimate overall survival in the BSC arm for the pNET population unexpectedly improved the ICER by [redacted]% even though the HR

increased (from 0.74 to 0.95) i.e. there was less OS benefit associated with cabozantinib. The same was observed when extrapolations for OS were used in the BSC arm for pNET, where the ICER improved, despite the OS improving in the comparator arm (e.g. using exponential function for OS in BSC in pNET decreases the LY gained by 76% but also decreased the ICER by [redacted]%). For the epNET population, the opposite was observed, where applying the ITT OS HR (from IPCW HR of 0.65 to 0.86) or the use of parametric extrapolation increased the ICER, though only a slight increase (of [redacted]%) was reported.

6.87 This appeared to be due to the higher costs accrued in the PD health state for BSC (driven by the cost of subsequent treatment) counteracting against the decrease in incremental QALYs. Additional multivariate sensitivity analyses were conducted during the evaluation to compare the cost of subsequent treatment under different scenarios. These analyses showed that once the proportion of patients receiving subsequent treatment post progression in the BSC arm was adjusted to be equal in both arms, the ICER in both models increased as expected when a less favourable OS HR was assumed.

6.88 Table 19 and Table 20 summarises the results of the stepped economic evaluation presented in the submission for pNET and epNET respectively.

Table 19: Results of the stepped economic evaluation (pNET)

Step and component	CBZ	BSC	Increment ($)
Step 1: Trial-based costs and outcomes (to median follow up (23 months))			
Costs (drug acquisition only)	$[redacted]	$0	[redacted]
LYG	1.65	1.54	0.10
Incremental cost/extra LY gained			[redacted] [1a]
Step 2: Extrapolation of PFS, OS and TTD to horizon			
Costs (drug acquisition only)	$[redacted]	$0	[redacted]
LYG	4.36	3.48	0.88
Incremental cost/extra LY gained			[redacted] [2 b]
Step 3: Inclusion of all costs			
Costs	$[redacted]	$127,168	[redacted]
LYG	4.36	3.48	0.88
Incremental cost/extra LY gained			[redacted] [3]
Step 4: Transformation of LYs to QALYs			
Costs	$[redacted]	$127,168	[redacted]
QALYs	3.06	2.31	0.75
Incremental cost/extra LY gained			[redacted] [4]
Step 5: Discounting at 5% pa			
Costs	$[redacted]	[redacted]	
QALYs	2.70	2.07	0.63
Incremental cost/extra QALY gained (base case)			[redacted] [4]
Pre-PBAC response revised base case			
Changes: DPMQ of $4,580; 7.5 year time horizon; half cycle correction removed for drug costs; same proportion of patients assumed to use post-progression therapies in the cabozantinib and BSC arms; and use of KM data for 12 months.			
Costs	$[redacted]	$101,125	[redacted]
QALYs	2.64	2.12	0.53
LYG	3.71	3.17	0.54
Incremental cost/extra QALY gained (base case)			[redacted] [2]

Source: Table 3-42, p204 of the submission.

BSC: best supportive care; CBZ: cabozantinib; epNET: extra-pancreatic neuroendocrine tumour; LY: life-years; OS: overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; QALY: quality-adjusted life year; TTD: time to treatment discontinuation

[a] Calculated by the submission using round numbers. This was $[redacted] in the economic model.

[b] Calculated by the submission using round numbers. This was $[redacted] in the economic model.

The redacted values correspond to the following ranges:

[1] *$355,000 to < $455,000*

[2] *$55,000 to < $75,000*

[3] *$35,000 to < $45,000*

[4] *$45,000 to < $55,000*

Table 20: Results of the stepped economic evaluation (epNET)

Step and component	CBZ	BSC	Increment
Step 1: Trial-based costs and outcomes (to median follow up (23 months))			
Costs (drug acquisition only)	$[redacted]	$0	$[redacted]
LYG	1.47	1.27	0.20
Incremental cost/extra LY gained			[redacted][1a]
Step 2: Extrapolation of PFS, OS and TTD to horizon			
Costs (drug acquisition only)	$[redacted]	$0	$[redacted]
LYG	2.85	1.88	0.97
Incremental cost/extra LY gained			[redacted][2b]
Step 3: Inclusion of all costs			
Costs	$[redacted]	$64,541	$[redacted]
LYG	2.85	1.88	0.97
Incremental cost/extra LY gained			[redacted][3]
Step 4: Transformation of LYs to QALYs			
Costs	$[redacted]	$64,541	$[redacted]
QALYs	1.80	1.16	0.64
Incremental cost/extra LY gained			[redacted][4]
Step 5: Discounting at 5% pa			
Costs	$[redacted]	$60,751	$[redacted]
QALYs	1.64	1.09	0.55
Incremental cost/extra QALY gained (base case)			[redacted][4]
Pre-PBAC response revised base case			
Changes: DPMQ of $3,552; 7.5 year time horizon; half cycle correction removed for drug costs; same proportion of patients assumed to use post-progression therapies in the cabozantinib and BSC arms; and use of KM data for 12 months			
Costs	$[redacted]	$55,729	$[redacted]
QALYs	1.60	1.10	0.50
LYG	2.49	1.78	0.71
Incremental cost/extra QALY gained (base case)			[redacted][4]

Source: Table 3-42, p204 of the submission.
Source: Table 3-42, p204 of the submission.
BSC: best supportive care; CBZ: cabozantinib; epNET: extra-pancreatic neuroendocrine tumour; LY: life-years; OS: overall survival; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; QALY: quality-adjusted life year; TTD: time to treatment discontinuation
[a] Calculated by the submission using round numbers. This was $[redacted] in the economic model.
[b] Calculated by the submission using round numbers. This was $[redacted] in the economic model.
The redacted values correspond to the following ranges:
[1] *$155,000 to < $255,000*
[2] *$25,000 to < $35,000*
[3] *$35,000 to < $45,000*
[4] *$55,000 to < $75,000*

6.89 The PBAC noted that the pre-PBAC response's revised base case estimated incremental life years gained of 0.54 and 0.71 in pNET and epNET, respectively. When Kaplan-Meier data were applied for 24 months (rather than 12 months) these remained relatively unchanged (0.55 and 0.70 incremental life years gained for pNET and epNET, respectively).

6.90 The results of key sensitivity analyses are summarised in Table 21 and Table 22, including multivariate sensitivity analyses addressing some of the key issues raised by the ESC. These are based on the submission's model (not the revised base case provided in the pre-PBAC response).

Table 21: Results of sensitivity analyses (pNET) based on the economic model provided with the submission

Scenario	Incr cost ($)	Incr QALY	ICER	% Δ
Base case	[redacted]	**0.63**	[redacted][1]	**-**
Time horizon: 10 years				
5 years	[redacted]	0.41	[redacted][2]	[redacted]%
A. 7.5 years	[redacted]	0.54	[redacted][1]	[redacted]%
Discount rate (costs and outcomes), 5% per year				
0%	[redacted]	0.75	[redacted][1]	-[redacted]%
3.5%	[redacted]	0.66	[redacted][1]	-[redacted]%
Half cycle correction applied to time on treatment				
B. Remove half cycle correction from time on treatment	[redacted]	0.63	[redacted][1]	[redacted]%
Extrapolation: Best-fitting approach for CBZ, adjusted HR applied for BSC				
C. KM data (up to 24 months) applied to CBZ arm (PFS, OS and TTD)	[redacted]	0.59	[redacted][2]	[redacted]%
CBZ PFS parametric distribution: Gompertz (conservative)		0.59	[redacted][2]	[redacted]%
BSC PFS method: parametric distribution, lognormal (best-fitting)		0.62	[redacted][1]	[redacted]%
CBZ OS parametric distribution: Weibull (more conservative)		0.57	[redacted][2]	[redacted]%
BSC OS method: parametric distribution, exponential (best-fitting)		0.29	[redacted][1]	-[redacted]%
BSC OS method: parametric distribution, loglogistic (alternative)		0.17	[redacted][1]	-[redacted]%
BSC OS survival method: ITT HR		0.26	[redacted][1]	-[redacted]%
CBZ TTD: PFS for TTD		0.62	[redacted][3]	[redacted]%
Utilities (PF: 0.819; PD: 0.650)				
CABINET and Swinburn utility values: PF: 0.819; PD: 0.612	[redacted]	0.64	[redacted][1]	-[redacted]%
Swinburn 2012 utility values: PF: 0.771; PD: 0.612		0.59	[redacted][1]	[redacted]%
Glover 2021 utility values for pNET: PF: 0.805; PD: 0.790		0.56	[redacted][2]	[redacted]%
Pavel 2017 utility values: PF: 0.779; PD:0.725		0.55	[redacted][2]	[redacted]%
Concurrent SSA use allowed (CBZ: 27.34% lanreotide, 27.34% octreotide; BSC: 27.42% lanreotide, 27.42% octreotide)				
No SSA use	[redacted]	0.63	[redacted][1]	-[redacted]%
Proportion of patients receiving additional therapy: CBZ: 51.02%; BSC: 62.07%				
D. Proportion of BSC pts receiving additional therapy: 51.02%	[redacted]	0.63	[redacted][2]	[redacted]%
Proportion of CBZ and BSC pts receiving additional therapy: 40%		0.63	[redacted][2]	[redacted]%
Proportion of BSC pts receiving additional therapy: 51.02% and ITT OS HR assumed		0.26	[redacted][3]	[redacted]%
Multivariate sensitivity analyses				
A+ B	[redacted]	0.54	[redacted][2]	[redacted]%
A+B+C		0.51	[redacted][2]	[redacted]%
A+B+C+D		0.51	[redacted][4]	[redacted]%

Source: Table untitled, p207 of the submission.

AE: adverse event; BSC: best supportive care; CBZ: cabozantinib; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; incr: incremental; ITT: intent-to-treat; KM: Kaplan-Meier; OS: overall survival; PD: progressed disease PF: progression free; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radiation therapy; pts: patients; QALYs: quality-adjusted life years; SSA: somatostatin analogue; TTD; time to treatment discontinuation

The redacted values correspond to the following ranges:

[1] *$45,000 to < $55,000*

[2] *$55,000 to < $75,000*

[3] *$95,000 to < $115,000*

[4] *$75,000 to < $95,000*

Table 22: Results of sensitivity analyses (epNET) based on the economic model provided with the submission

Scenario	Incr cost ($)	Incr QALY	ICER	% Δ
Base case	$[redacted]	**0.55**	[redacted][1]	**-**
Time horizon: 10 years				
5 years	[redacted]	0.40	[redacted][2]	[redacted]%
A. 7.5 years	[redacted]	0.49	[redacted][1]	[redacted]%
20 years	[redacted]	0.63	[redacted][1]	[redacted]%
Discount rate (costs and outcomes), 5% per year				
0%	[redacted]	0.64	[redacted][1]	-[redacted]%
3.5%	[redacted]	0.57	[redacted][1]	-[redacted]%
Half cycle correction applied to time on treatment				
B. Remove half cycle correction from time on treatment	$41,188	0.55	[redacted][2]	[redacted]%
Extrapolation: Best-fitting approach for CBZ, adjusted HR applied for BSC				
C.KM data (up to 24 months) applied to CBZ arm (PFS, OS and TTD)	[redacted]	0.53	[redacted][2]	[redacted]%
CBZ PFS parametric distribution: Weibull (conservative)	[redacted]	0.53	[redacted][2]	[redacted]%
BSC PFS method: parametric distribution, lognormal (best-fitting)	[redacted]	0.54	[redacted][1]	[redacted]%
CBZ OS parametric distribution: Weibull (conservative)	[redacted]	0.42	[redacted][2]	[redacted]%
BSC OS method: parametric distribution, loglogistic (best-fitting)	[redacted]	0.26	[redacted][1]	[redacted]%
BSC OS method: ITT HR	[redacted]	0.26	[redacted][1]	[redacted]%
CBZ TTD: PFS for TTD	[redacted]	0.55	[redacted][3]	[redacted]%
Utilities (PF: 0.731; PD: 0.580)				
CABINET and Swinburn utility values: PF: 0.731; PD: 0.612	[redacted]	0.55	[redacted][1 a]	-[redacted]%
Swinburn 2012 utility values: PF: 0.771; PD: 0.612	[redacted]	0.58	[redacted][1]	-[redacted]%
Glover 2021 utility values for epNET: PF: 0.793; PD: 0.740	[redacted]	0.62	[redacted][1]	-[redacted]%
Pavel 2017 utility values: PF: 0.779; PD:0.725	[redacted]	0.61	[redacted][1]	-[redacted]%
Concurrent SSA use allowed (CBZ: 34.33% lanreotide, 34.33% octreotide; BSC: 34.78% lanreotide, 34.78% octreotide)				
No SSA use	[redacted]	0.55	[redacted][1]	-[redacted]%
Proportion of patients receiving additional therapy: CBZ: 45.05%; BSC: 66.67%				
D.Proportion of BSC pts receiving additional therapy: 45.05%	[redacted]	0.55	[redacted][2]	[redacted]%
Proportion of CBZ and BSC pts receiving additional therapy: 40%	[redacted]	0.55	[redacted][2]	[redacted]%
Proportion of BSC pts receiving additional therapy: 45.05% and ITT OS HR assumed	[redacted]	0.26	[redacted][4]	[redacted]%
Multivariate sensitivity analyses				
A+ B	[redacted]	0.49	[redacted][2]	[redacted]%
A+B+C	[redacted]	0.47	[redacted][2]	[redacted]%
A+B+C+D	[redacted]	0.47	[redacted][2]	[redacted]%

Source: Table untitled, p207 of the submission.

AE: adverse event; BSC: best supportive care; CBZ: cabozantinib; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; incr: incremental; ITT: intent-to-treat; KM: Kaplan-Meier; OS: overall survival; PD: progressed disease PF: progression free; PFS: progression-free survival; pNET: pancreatic neuroendocrine tumour; PRRT: peptide receptor radiation therapy; pts: patients; QALYs: quality-adjusted life years; SSA: somatostatin analogue; TTD; time to treatment discontinuation

[a] Assumed erroneously reported by the submission as $[redacted], corrected during the evaluation.

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$75,000 to < $95,000*

[3] *$95,000 to < $115,000*
[4] *$115,000 to < $135,000*

6.91 The ESC advised the model structure was reliable for decision-making, but that there were key uncertainties with the following model parameters: time horizon; modelling of OS in the BSC arm (including lack of use of KM data); modelling of subsequent therapies; and application of the half-cycle correction for drug costs.

6.92 The pre-PBAC response made the following changes to the economic model: revised indication specific DPMQs were applied; the time horizon was reduced to 7.5 years (from 10 years); the half cycle correction was removed for drug costs; the proportion of patients receiving post-progression therapy was assumed to be the same in the cabozantinib and BSC arms; and Kaplan-Meier data were applied for 12 months (for OS, PFS and time on treatment).

Cost minimisation approach

6.93 For the third line setting, the submission presented a CMA based on the claim of non-inferior efficacy between cabozantinib versus sunitinib (pNET), and versus chemotherapy (epNET).

6.94 For the treatment of pNET in the third line setting, the equi-effective doses were estimated as:

- cabozantinib 42.37 mg daily = sunitinib 33.52 mg daily (both until progression or high toxicity).

6.95 The estimated mean dose of cabozantinib per day of 42.37 mg was based on cabozantinib utilisation in CABINET for patients with pNET. The draft product information states that treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. The sunitinib dose was based the mean dose of sunitinib for the treatment of pNET using PBS utilisation data from July 2023 to June 2024. Sunitinib is supplied in packs of 28 at strengths of 12.5 mg, 25 mg, 37.5 mg and 50 mg. PBS utilisation data for the item numbers applicable to pNET indicated utilisation of 6%, 34%, 47% and 14%, respectively, across the strengths (including both initial and continuing scripts). The resulting weighted average strength was 33.52 mg. The PBS listing for continuing sunitinib requires that patients have not progressed while on treatment.

6.96 The estimation of equi-effective doses was based on the cost of treatment per day (assuming the same duration of treatment in each arm). The use of a cost per daily dose was consistent with the method used to establish the equi-effective doses for everolimus and sunitinib (everolimus 8.59 mg daily and sunitinib 34.24 mg daily; paragraph 6.13, everolimus PSD, March 2014 PBAC meeting), and the ESC considered this was reasonable.

6.97 For the treatment of epNET at the third line setting, the equi-effective doses were estimated as:

- cabozantinib 43.13 mg daily = chemotherapy at standard doses (both until progression or high toxicity).

6.98 The estimated mean dose per day of 43.13 mg was based on cabozantinib utilisation in CABINET for patients with epNET.

6.99 The submission assumed chemotherapy at standard doses would be 50% use of CAPTEM and 50% use of FOLFOX. However, the ESC considered that CAPTEM is more widely used than FOLFOX given the administration requirements of FOLFOX. The ESC noted that sensitivity analyses explored the impact of a 75% : 25% CAPTEM : FOLFOX utilisation ratio (Table 25). The PBAC agreed with the ESC that CAPTEM is more widely used in clinical practice, and considered that a utilisation ratio of 60% CAPTEM to 40% FOLFOX may be more reasonable.

6.100 For CAPTEM, the equi-effective dosages were based on the eviQ guidelines (eviQ 1784v6), which lists the treatment schedule as capecitabine 750 mg/m^2 taken orally twice a day on days 1-14 and temozolomide 100 mg/m^2 taken orally twice a day on days 10-14 in 28-day cycles. The submission claimed that this is consistent with the product information for these medicines.

6.101 The submission did not provide a mean dose for CAPTEM. While these doses are consistent with the eviQ guidelines, the eviQ guidelines also state "(consider lower doses (capecitabine 600 mg/m^2 BD and temozolomide 75 mg/m^2 BD) if extensive prior chemotherapy/radiation therapy." The evaluation considered that it was unclear what proportion of patients would use the lower doses; however, it was possible that the dosage of capecitabine and temozolomide may be overestimated in the CMA. Additionally, neither capecitabine nor temozolomide are indicated for the treatment of epNET and their recommended dosages for other indications were variable. Overall, the evaluation and the ESC considered that the doses assumed for CAPTEM in the CMA for epNET (and therefore the cost) may be uncertain and possibly overestimated.

6.102 For FOLFOX, no eviQ guidelines or any other treatment guidelines were identified in the submission that are specific to NETs. Therefore, the submission used the regimen described by Faure 2017, claiming that this is the only published report to describe details of the regimen in NETs and that it is consistent with several eviQ guidelines for GI cancers. The regimen described by Faure 2017 is comprised of a 14-day cycle with IV infusions of oxaliplatin (85 mg/m^2) and folinic acid (100 mg/m^2) day 1 followed by two IV administrations of fluorouracil for 10 minutes (400 mg/m^2) and then a 46-hour continuous infusion (2,400 mg/m^2). This regimen is consistent with several eviQ guidelines for GI cancers (e.g., eviQ guidelines 637v11, 114v10 and 3931v3) with the exception of the folinic acid dose which was listed as 50 mg in the eviQ guidelines. The eviQ guidelines noted that this dose had been changed from 200mg/m^2 based on reference committee consensus. As for CAPTEM, the submission did not provide a mean dose for FOLFOX. While the FOLFOX dosages used in the CMA are consistent with those proposed by Faure 2017, these are recommended dosages rather than

what patients have received. Consequently, the evaluation considered that the dosages of FOLFOX included in the CMA were uncertain and possibly overestimated.

6.103 For the treatment of pNET at the third line setting, the submission reasonably did not include any additional costs or cost offsets in the CMA for cabozantinib or sunitinib. Testing recommendations were generally comparable for cabozantinib and sunitinib.

6.104 For the treatment of epNET at the third line setting, as cabozantinib and CAPTEM are dosed orally, no associated administration costs were applied in the CMA. FOLFOX is administered by intravenous infusion on day 1 of a 14-day treatment cycle and therefore the cost of MBS item number 13950 (parenteral administration of one or more antineoplastics; $123.05 [100% benefit]) was incorporated into the CMA for each day of infusion. No cost-offsets for the management of safety and toxicity were included in the CMA.

6.105 The submission claimed that, in the absence of higher quality data for chemotherapy in epNET, it was reasonable to conclude that CAPTEM and FOLFOX both provide a median PFS of approximately 10 months and this duration was used to estimate the time on treatment with chemotherapy in the CMA. This was based on the largest study included in the submission's retrospective case series, Al-Toubah 2021 (n=132; conducted in patients with nonpancreatic primary tumours). However, as shown in Table 9, in epNET, the median PFS for CAPTEM ranged from 6.4 to 15.3 months and for FOLFOX, median PFS ranged from 4 to 14.1 months. The evaluation and the ESC considered it was highly uncertain whether the assumed treatment duration of 10 months was reasonable for both CAPTEM and FOLFOX for the treatment of epNET.

6.106 The submission stated that for consistency, the median PFS from CABINET of 8.48 months in patients in the epNET cohort was applied to approximate the duration of treatment with cabozantinib. The submission claimed that this was a conservative assumption, as the median duration of treatment in CABINET for cabozantinib was 5.37 months. While the CMA was based on the therapeutic claim that the effectiveness of cabozantinib is non-inferior to chemotherapy (CAPTEM/FOLFOX), the submission assumed different durations of PFS (used as a proxy for treatment), which indicated a difference in efficacy given both are generally treat-to-progression therapies, with chemotherapy (PFS=10 months) being superior to cabozantinib (8.48 months). A sensitivity analysis assuming the same treatment duration (with the implication that PFS was equal for both treatments) was conducted during the evaluation. The ESC and the PBAC considered that the CMA should assume the same treatment durations for chemotherapy (CAPTEM and FOLFOX) and cabozantinib. The pre-PBAC response stated that the revised weighted price was updated to reflect this change (refer to Table 14).

6.107 The results of the CMA are presented in Table 23 and Table 24 for the pNET and epNET populations, respectively. For pNET, the submission used the DPMQ for sunitinib with prices effective as of 1/1/2025. During the evaluation, prices were updated to reflect recent price changes (effective 1/4/2025). Additionally, the AEMPs for sunitinib were

used to calculate the price of cabozantinib rather than DPMQs (as used in the submission), to exclude pharmacy mark-ups and dispensing fees (which differed based on strength for sunitinib) from the CMA calculations. The applicable fees were added to the cabozantinib AEMP after the CMA calculations.

Table 23: Results of the cost-minimisation (pNET)

Sunitinib				Cabozantinib			
PBS Item number	**Strength**	**Use**	**AEMP**		**Strength**	**AEMP**	**DPMQ**
10004M, 10009T	12.5 mg	6%	$513.55		60 mg		
2842N, 2959R	25 mg	34%	$1,033.58		40 mg		
10464R, 10473F	37.5 mg	47%	$1,549.06		20 mg	**$1,487.68**	$1,627.37 [a]
2837H, 10010W	50 mg	14%	$2,092.68				
Pack size	28			Pack size	30		
Average dose	33.52 mg			Average dose	42.37 mg		
Weighted price	$1,388.51						
Cost per day	$49.59			Cost per day		**$49.59**	

AEMP: approved ex-manufacturer price; DPMQ: dispensed price for maximum quantity

[a] DPMQ calculated based on community pharmacy markups.

Source: Table 3-6, p148 of the submission and sheet 'Pricing Framework', Cabozantinib in NETs CEA Section 3.xlsm

Table 24: Results of the cost-minimisation (epNET)

FOLFOX			**Cabozantinib**	
Oxaliplatin total dose per treatment course	3,525 mg		Cabozantinib total dose per treatment course	11,119 mg
Folinic acid total dose per treatment course	4,147 mg			
Fluorouracil total dose per treatment course	116,128 mg[a]		60/40/20 mg	
AEMP drug cost per administration	$471.37		Cost of administration	Nil
Cost of administration	$123.05		Days per pack	30
Doses per 28-day cycle	2			
Total cost per 28-day cycle	$1,188.84			
Proportion of use	50%			
Median PFS (months)	10		Median PFS (months)	8.48
Cost per treatment course	$12,907.41			
CAPTEM				
DPMQ drug cost for 28 days	$276.80			
Proportion of use	50%			
Median PFS (months)	10			
Cost per treatment course	$3,005.20			
Chemotherapy				
Weighted cost per treatment course	$7,956.30			
Cost per course (dispensed price)	$7,956.30		$7,956.30	$7,956.30
Cabozantinib price required for cost-minimisation, DPMQ for 30 tablets				$925.90

AEMP: approved ex-manufacturer price; DPMQ: dispensed price for maximum quantity

[a] In the submission, it was assumed that patients receiving 5-fluorouracil required 4,584 mg (based on BSA of 1.91 m2), which was administered as two 500 mg + four 1,000 mg. During the evaluation this was changed to one 5,000 mg injection.

Source: Table 3-11, p155 of the submission.

6.108 A sensitivity analysis was conducted during the evaluation using everolimus as the comparator in pNET. Based on PBS usage between January 2024 to December 2024 of everolimus 5 mg and 10 mg, a weighted dose of 7.07 mg/day was estimated which was associated with a daily cost of $40.22, leading to a 19% reduction in the price of cabozantinib. However, if 8.59 mg of everolimus was used (the equi-effective doses of

everolimus 8.59 mg daily and sunitinib 34.24 mg daily were established in paragraph 6.13, everolimus PSD, March 2014 PBAC meeting) the price of cabozantinib would decrease by 1.5%.

6.109 For epNET, as the treatment duration for CAPTEM and FOLFOX, the ratio of CAPTEM:FOLFOX and the doses of the individual drugs for CAPTEM used in the CMA were associated with a high degree of uncertainty, their impact was explored in sensitivity analyses, conducted during the evaluation (Table 25). The sensitivity analyses indicated that the CMA price of cabozantinib is sensitive to the assumed duration of treatment for chemotherapy and cabozantinib, and to the ratio of CAPTEM to FOLFOX.

Table 25: Sensitivity analyses (epNET)

Analysis	AEMP	% change
Base case	**$925.90**	
Duration of treatment for chemotherapy (BC: 10 months) and cabozantinib (BC: 8.48 months)		
Duration of treatment for chemotherapy same as cabozantinib (8.48 months)	$785.16	-15.2%
Duration of treatment for cabozantinib same as chemotherapy (10 months)	$785.16	-15.2%
Treatment duration for CAPTEM and FOLFOX = 15.3 months (Crespo 2017)	$1,416.62	+53.0%
Duration of treatment for cabozantinib same as chemotherapy (15.3 months)	$785.16	-15.2%
Chemotherapy ratio of CAPTEM:FOLFOX (BC: 50:50)		
CAPTEM:FOLFOX (75:25)	$637.81	-31.1%
CAPTEM:FOLFOX (60:40);	$810.66	-12%
CAPTEM dose (BC: capecitabine 750 mg/m^2 BD and temozolomide 100 mg/m^2 BD)		
All patients take CAPTEM lower dose (capecitabine 600 mg/m2 BD and temozolomide 75 mg/m2 BD)[a]	$901.84	-2.6%
Fluorouracil vials used for 2,400mg/m^2 dose (BC: two 500 mg vials + four 1,000 mg)		
Fluorouracil: one 5 g vial	$907.69	-2.0%
CAPTEM:FOLFOX (60:40); plus duration of treatment for chemotherapy same as cabozantinib (8.48 months)	$687.44	-26%

AEMP = approved ex-manufacturer price; BC = base case; BD = twice daily, TTD = time to discontinuation

[a] *Lower dose assumed patients took temozolomide 1x140mg and capecitabine 3x500mg.

Source: Calculated during evaluation using sheet 'Pricing Framework', Cabozantinib in NETs CEA Section 3.xlsm

Drug cost/patient

6.110 The drug cost per patient per month or per course are summarised in Table 26 and Table 27. These are based on the price and parameters proposed in the submission (rather than the revisions proposed in the pre-PBAC response). Differences in the cost of cabozantinib in pNET compared to epNET in the CUA and the financial estimates were due to differences in the duration of treatment as well as the assumed compliance/dose holds.

Table 26: Drug costs in pNET based on the price and parameters proposed in the submission

	Cabozantinib				Comparator			
	Trial	CUA 4L	CMA 3L	Financial estimates	Trial	CUA	CMA	Financial estimates
Mean dose	42.37 mg/day	60mg/day with dose hold of 7.7%	42.37 mg/day	Initiation: 42.8mg/day [a] Continuation: 34.9mg/day [a]	-	-	sunitinib 33.52mg/day	Sunitinib: 33.48mg/day [b] Everolimus" 7.07mg/day [b]
Mean duration	9.36 months	12.51 months	until progress	12.51 months	4.4 months	4.82 months	until progress	12.51 months
Cost/patient/ month or /course	-	$[redacted]/ course	$18,100/ year [c]	$36,477/ patient year [d]	-	-	$18,100/ year [c]	Sunitinib $17,926/ patient year [e] $13,978/ patient year [e]

Source: Calculated during the evaluation

AEMP = approved ex-manufacturer price; CMA = cost minimisation approach, CUA = cost utility analysis; DPMQ = dispensed price for maximum quantity

[a] Calculated based on assumed proportion of use of 20mg, 40mg and 60mg cabozantinib scripts in financial estimates, does not include compliance/dose holds

[b] Calculated based on proportion of PBS use of sunitinib 12.5mg, 25mg, 37.5mg and 50mg and everolimus 5mg and 10mg on the PBS for Jan 2024 to Dec 2024

[c] Daily cost of $49.59 multiplied by 365 days

[d] Total cost for cabozantinib in pNET net of copayments divided by total patient years of treatment in financial model, accounting for 92.3% compliance

[e] Total cost for sunitinib or everolimus offset (adjusted for proportion of use on the PBS for Jan 2024 to Dec 2024) net of copayments divided by total patient years of treatment offset in financial model, accounting for 92.3% compliance. Sunitinib cost differed to CMA due to use of DPMQ instead of AEMP used and compliance adjustments in financial adjustments. Everolimus cost was much lower than CMA due to use of DPMQ instead of AEMP, compliance adjustments and a lower average daily dose (7.07mg/day) compared to the accepted equi-effective dose by the PBAC (8.59mg/day)

Table 27: Drug costs in epNET based on the price and parameters proposed in the submission

	Cabozantinib				Comparator			
	Trial	CUA 4L	CMA 3L	Financial estimates	Trial	CUA	CMA	Financial estimates
Mean dose	43.13 mg/day	60mg/day with dose hold of 10.8%	42.37 mg/day	Initiation: 42.8mg/day [a] Continuation: 34.9mg/day [a]	-	-	FOLFOX and CAPTEM (see paragraphs 6.98 and 6.102 for dosage)	
Mean duration	6.85 months	8.62 months	8.48 months	8.62 months	4.29 months	5.13 months	10 months	10 months
Cost/patient/ month or /course	-	$[redacted]/ course	$7,956/ course	$35,191/ patient year [b]	-	-	$7,956/ course	FOLFOX $7,735/course [c] CAPTEM $2,468/course [c]

Source: Calculated during the evaluation

CMA = cost minimisation approach, CUA = cost utility analysis

[a] Calculated based on assumed proportion of use of 20mg, 40mg and 60mg cabozantinib scripts in financial estimates, does not include compliance/dose holds

[b] Total cost for cabozantinib in epNET net of copayments divided by total patient years of treatment in financial model, accounting for 89.2% compliance

[c] Total cost for FOLFOX or CAPTEM (50:50 assumed), net of copayments, divided by number of patients 3L epNET initiating patients, accounting for 89.2% compliance. Differed to CMA due to lower compliance and no MBS items considered for FOLFOX.

Estimated PBS usage & financial implications

6.111 This submission was not considered by DUSC.

6.112 The submission adopted an epidemiological approach. The evaluation considered that a market-share approach for the third line setting for pNET may have been appropriate as cabozantinib may substitute for PBS-listed sunitinib and everolimus in some patients although it may represent an additional treatment line in other patients.

6.113 Table 28 outlines the key inputs relied on in the financial estimates.

Table 28: Key inputs for financial estimates

Parameter	Value and Source	Comments
Eligible Population		
Prevalence of NEN	Yr 1 (2025): [redacted][1] Yr 2 (2026): [redacted][1] Yr 3 (2027): [redacted][1] Yr 4 (2028): [redacted][1] Yr 5 (2029): [redacted][1] Yr 6 (2030): [redacted][1] The age-standardised 5-year prevalence of NEN from the AIHW Cancer Data in Australia 2024 was 53.2 per 100,000, however, the submission claimed that this average was dragged down by the very low rates of NEN observed in the age cohorts below 18 years of age. Instead, an age standardised rate for people aged ≥18 years was calculated. Age specific rates for each 10 year+ bracket (15-24 up to 85+) were applied to the ABS population for each age bracket, then a flat prevalence of 66.14 per 100,000 was estimated. This was applied as a flat rate to the ≥18 ABS population projections (2025-2030).	The evaluation considered that the estimated age standardised rate for people aged ≥18 years was uncertain. In the calculation of the ≥18 age standardised prevalence rate, the age specific prevalence rate of people ages 15-24 years was applied to the 18–24-year ABS population, which the evaluation considered increased uncertainty.
Proportion of prevalent NEN patients with pNET	9% 5-year prevalence to 31 July 2020 from AIHW Cancer Data in Australia 2024. (Prevalence of pNET / prevalence of NEN)	Reasonable, although the evaluation noted that Wyld 2019 may be an alternative source (refer to paragraph 6.70).
Proportion of prevalent NEN patients with epNET	54% Prevalence of epNET was calculated from the reported prevalence of NET and pNET (i.e. epNET = NET – pNET)	Reasonable, although the evaluation noted that Wyld 2019 may be an alternative source (refer to paragraph 6.70).
Proportion with stage IV disease	pNET: 37.16% and epNET: 25.72% Source: White 2022. White 2022 was UK cancer registry study (n=63,949 NEN tumours; 1995-2018).	This was likely reasonable. However, the generalisability to the target PBS population was uncertain.

Parameter	Value and Source	Comments
Proportion of patients at 3rd or 4th line treatment	24% receive 3rd line treatment 14% receive 4th line treatment Proportion of patients at each line of therapy was calculated from US hospital databases published in Dasari 2019 (Lung NET; three centres; n=83) and Kulke 2019 (GI NET; four centres; n=273). Bodei 2017, which reported the incidence of difference types of NETs was also used in the financial workbook to weight the results by location of NET (GI NET vs Lung). (i.e. the financial estimates assumed that 24% of prevalent patients with Stage IV pNET or epNET would be eligible for cabozantinib in 3L. Uptake rates were then applied to this estimate. Similarly, 14% of prevalent patients with Stage IV pNET or epNET would be eligible for cabozantinib in 4L. This resulted in a total of 38% of patients with Stage IV pNET or epNET assumed to be eligible for cabozantinib in either 3L or 4L, with uptake rates then applied.)	The evaluation considered that the proportions were uncertain. The treatment patterns observed from retrospective chart reviews in the US (total of seven centres) may not be generalisable to Australian clinical practice or the PBS population and therefore were uncertain. Dasari 2019 excluded patients with poorly differentiated histology or carcinomas, which have poorer prognosis than well differentiated NETs. Likewise, Kulke 2019 also excluded patients with poorly differentiated histology. This was consistent with the requested restriction which specifies that patients must have well differentiated disease. The PBAC considered that the estimates applied in the submission were reasonable in the absence of alternative data. However, the PBAC noted that Dasari 2019 and Kulke 2019 also reported a further 7% and 4% of patients receive treatment in fifth line and sixth line respectively. While these may represent the same patients who received treatment in fourth line, the PBAC considered this supported the use of high uptake rates in the fourth line setting, particularly from Year 3 onwards.
Treatment utilisation (Cabozantinib)		

Parameter	Value and Source	Comments
Uptake	<table><tr><td>Initiation therapy</td><td></td></tr><tr><td>Prevalent pNET – 3L</td><td>[redacted]%</td></tr><tr><td>Prevalent pNET – 4L</td><td>[redacted]%</td></tr><tr><td>Prevalent epNET – 3L</td><td>[redacted]%</td></tr><tr><td>Prevalent epNET – 4L</td><td>[redacted]%</td></tr><tr><td>Continuing therapy</td><td></td></tr><tr><td>pNET cohort</td><td>[redacted]%</td></tr><tr><td>epNET cohort</td><td>[redacted]%</td></tr></table> Uptake rates were flat across the six-year financial period. Source: The % of eligible patients initiating therapy was based on Sponsor assumption. The continuing therapy rates were based on the disease control rate from CABINET by BICR; the sum of CR, PR and Stable disease was used. i.e. pNET= 0% CR + 19% PR + 61% SD = 80% epNET= 0% CR + 5% PR + 65% SD = 70%	The evaluation considered that the flat uptake rate of [redacted]%, commencing year 1, for 3L initiation therapy in the pNET population was likely overestimated as SUN/EVE are established PBS listed therapies for pNET patients, and pNET patients would be able to access CBZ following SUN/EVE therapy (but not vice versa) based on the requested restriction. Therefore, the evaluation considered that it was uncertain to what degree patients & clinicians would opt for CBZ as 3L treatment (if at all), as this reduces the number of treatment options. The evaluation considered that the flat uptake rate of [redacted]%, commencing year 1, for 3L initiation therapy in the epNET population may be an underestimate as CBZ would be the only PKI available for epNET. Conversely, the evaluation considered that the uptake rate for 4L initiation therapy (especially in incident patients) for epNET was likely overestimated, as these patients would be expected to receive CBZ in 3L. However, the PBAC considered that the 4L cohort may also receive treatment in fifth and subsequent lines (as outlined in the row above) with relatively high uptake, particularly given the absence of alternative options. Overall, the PBAC considered that utilisation of cabozantinib was likely to be more common in 4L (or later) than in 3L, and that the ratio of patients initiating cabozantinib in the financial estimates should be around [redacted]% in 3L versus [redacted]% in 4L, consistent with the calculation of the weighted price

Parameter	Value and Source	Comments
Treatment Utilisation (Affected medicines)		
Uptake	The uptake rates for affected medicines were assumed to be the same as cabozantinib.	Consistent with the CMA presented by the submission. In the CMA and the CUA, the submission assumed that a proportion of epNET patients would receive chemotherapy post 4L setting instead of at 3L. The level of chemotherapy offsets was therefore uncertain as for some patients, chemotherapy may just be displaced to a later line of therapy. The evaluation considered that the introduction of CBZ for epNET may grow the market given the lack of treatment options and some patients who may not elect to receive chemotherapy, may choose CBZ.
Costs		
Cost of Proposed medicine	$9472.60 DPMQ (published) $[redacted] DPMQ (effective)	Consistent with price proposed in the submission, however the PBAC's advised revised inputs for the derivation of the weighted price.
Cost of Affected medicines	DPMQs for non-EFC medicines were extracted from the PBS. The dispensed prices for oxaliplatin and fluorouracil (EFC medicines) were calculated from the effective AEMPs, Including private markup of 1.4%, private dispensing fee of $134.80, and public dispending fee of $90.13.	The DPMQs for sunitinib were updated during the evaluation to reflect current PBS listings, as a price reduction had occurred following the time of submission. In 3L epNET, the ESC considered that CAPTEM was more likely to be replaced than FOLFOX. The PBAC considered that [redacted]% of patients would otherwise use CAPTEM and 40% would otherwise use FOLFOX in this setting, consistent with the assumptions advised for the CMA. The PBAC also considered that, in the 3L epNET setting, the duration of therapy with CAPTEM and FOLFOX (i.e. the affected medicines) should be consistent with cabozantinib, per the assumptions advised for the CMA (i.e. 8.48 months).

<table>
<tr><th>Parameter</th><th>Value and Source</th><th>Comments</th></tr>
<tr><td>MBS items for CBZ</td><td>
<table>
<tr><th></th><th>MBS Item</th><th>MBS fee (100%)</th></tr>
<tr><td>Liver function tests</td><td>66512</td><td>$17.70</td></tr>
<tr><td>Complete blood count</td><td>65070</td><td>$16.95</td></tr>
<tr><td>Serum electrolytes/urea/creatine</td><td>66509</td><td>$15.65</td></tr>
<tr><td>Thyroid function test</td><td>66719</td><td>$34.80</td></tr>
<tr><td>Pharmacological stress ECHO</td><td>55145</td><td>$534.45</td></tr>
<tr><td>ECG</td><td>11729</td><td>$173.40</td></tr>
</table>
Increased utilisation of the above MBS services was considered for CBZ patients in the 4L setting only and was assumed to be the same across the pNET and epNET population.

The submission considered that patients treated with SUN/EVE or chemotherapy would already be subjected to a similar number of pathology monitoring interventions, and therefore increased MBS utilisation was not included in the 3L setting as substituting CBZ for current 3L treatments was unlikely to have any appreciable impact on costs.

It was assumed that liver function test, blood count and electrolytes/urea/creatinine are evaluated 3 times per patient year. Thyroid function tests, pharmacological stress ECHO and ECG were assumed to be assessed once (at commencement of CBZ treatment).</td><td>This was inconsistent with the submission's CUA, which did not account for additional costs associated with the use of CBZ. Background health costs considered in the CUA were the same between treatment arms and differed by health state and population (pNET/epNET).

For the third line setting, the CMA did not include any additional costs or cost offsets for cabozantinib versus sunitinib, nor chemotherapy. This was consistent with the financial model.

The calculation for increased cost to MBS services (Cells F16:K24 '7. Net changes – MBS') did not include multi-channel ECG costs, though this item was included in volume increases (Rows 73 and 74). This was corrected during the evaluation so that the estimated ECG costs were included.</td></tr>
<tr><td>Administration</td><td>Administration of intravenous cytotoxic chemotherapy is reimbursed under MBS Item number 13950 at a rate of $123.05 (100% fee). This was applied once per FOLFOX cycle.</td><td>Reasonable.</td></tr>
</table>

Source: Compiled during evaluation using information from Table 4-1, Table 4-3, and pp213-223 of the submission, and the submission's financial model workbook.

Abbreviations: 3L = third line; 4L = fourth line; AE = adverse event; AEMP = approved ex-manufacturer price; BSA = body surface area; CBZ = cabozantinib; CMA = cost-minimisation approach; CR = complete response; DTG = duration of treatment group; ECG = electrocardiogram; ECHO = echocardiogram; epNET = extra-pancreatic neuroendocrine tumours; EVE = everolimus; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PKI = protein kinase inhibitor; pNET = pancreatic neuroendocrine tumours; PR = partial response; RDI = relative dose intensity; RPBS = Repatriation Pharmaceutical Benefits Scheme; SD = stable disease; SUN = sunitinib

The redacted values correspond to the following ranges:

[1] 10,000 to < 20,000

6.114 The estimated financial impact of PBS listing cabozantinib is summarised in Table 29. The following were corrected during the evaluation in the submission's financial model and the PSCR stated that these changes were accepted by the sponsor:

- The price of sunitinib was updated to reflect the current PBS listing, as a price reduction had occurred since the time of submission;
- The submission calculated population splits for initiation and continuation across cabozantinib tablet strengths using the total number of PBS services (i.e. initial + continuing) as the denominator. This resulted in fewer than one script

per patient which substantially underestimated cabozantinib scripts. This was corrected so that the population split across strengths was calculated for the initiation and continuing scripts independently. A similar adjustment was made for sunitinib and everolimus offsets; and

- The calculation for increased cost to MBS services did not include multi-channel ECG costs, though this item was included in volume increases. This was corrected during the evaluation so that the estimated ECG costs were included.

Table 29: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Prevalent NET patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pNET (9%) [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of 3L treatment ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of 4L treatment ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total initiating pNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total continuing pNET ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
epNET (54%) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of 3L treatment ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of 4L treatment ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total initiating epNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total continuing epNET ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total initiating patients (pNET+ epNET)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total continuing patients (pNET+epNET)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts (pNET+epNET) [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3L pNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4L pNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3L epNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4L epNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of cabozantinib						
PBS and RPBS cost less co-pay (effective) [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3L pNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4L pNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3L epNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4L epNET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for other medicines						
SUN/EVE offset patients (same as initiating 3L pNET)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUN scripts [e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EVE scripts [f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy offset patients (same as initiating 3L epNET)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy scripts [g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total offset scripts (SUN+EVE+chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBS/RPBS cost less co-pay Total offset costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
SUN+EVE (3L pNET)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Chemotherapy (3L epNET)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net financial implications						
Net cost to PBS/RPBS (effective)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
3L pNET	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
4L pNET	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
3L epNET	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
4L epNET	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net cost to PBS/RPBS/MBS	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
3L pNET	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
4L pNET	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
3L epNET	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
4L epNET	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]

Source: Compiled during evaluation using information from Table 4-4, p216 of the submission, and the submissions financial workbook.
3L: third line; 4L: fourth line; CIV: continuous intravenous infusion; epNET: extra-pancreatic neuroendocrine tumours; EVE: everolimus; incl.: including; IV: intravenous; PBS: pharmaceutical benefits scheme; pNET: pancreatic neuroendocrine tumour; RPBS: repatriation pharmaceutical benefits scheme; SUN: sunitinib.

[a] Assumed 37% have stage IV disease, 24% entering 3L treatment, 14% entering 4L treatment

[b] Assumed 26% have stage IV disease, 24% entering 3L treatment, 14% entering 4L treatment

c Calculated depending on:

Initiating patients: Calculated using patient years of treatment using a 3 month initiation period. 11.24 scripts per year of treatment (365.25 days / (30 pack / (dosing of 1 tablet per day))* 92.30% compliance.

Continuing pNET patients: Calculated using patient years of treatment using a 9.51 month continuing period. 11.24 scripts per year of treatment (365.25 days / (30 pack / (dosing of 1 tablet per day))* 92.30% compliance.

Continuing epNET patients: Calculated using patient years of treatment using a 5.62 month continuing period. 11.24 scripts per year of treatment (365.25 days / (30 pack / (dosing of 1 tablet per day))* 92.30% compliance.

[d] A flat pricing arrangement for different strengths of cabozantinib (20mg, 40mg, 60mg) was applied. The published and effective DPMQs for cabozantinib were $9,472.60 and [redacted] per 30 tablet pack, respectively.

[e] Calculated using patient years of treatment using an 9.51 month continuing period. 12.04 scripts per year of treatment (365.25 days / (28 pack / (dosing of 1 tablet per day))* 92.30% compliance.

f Calculated using patient years of treatment using an 9.51 month continuing period. 11.24 scripts per year of treatment (365.25 days / (30 pack / (dosing of 1 tablet per day))* 92.30% compliance.

g Includes scripts for: capecitabine 500mg tablet, temozolomide 180mg capsule, oxaliplatin 200ng/40mL injection, folinic acid (leucovorin) 50mg/5mL injection, fluorouracil IV 1000mg/20mL injection, fluorouracil CIV injection. It was assumed that there would be a 50:50 split between CAPTEM (capecitabine and temozolomide) and FOLFOX (oxaliplatin, folinic acid (leucovorin), fluorouracil IV, fluorouracil CIV) regimens. 10-month treatment duration assumed.

The redacted values correspond to the following ranges:

[1] 10,000 to < 20,000

[2] 500 to < 5,000

[3] < 500

[4] 5,000 to < 10,000

[5] $10 million to < $20 million

[6] $0 to < $10 million

[7] net cost saving

6.115 The submission estimated the net cost to the PBS/RPBS/MBS of listing cabozantinib for NETs would be $10 million to < $20 million in Year 1, increasing to $10 million to < $20 million in Year 6. The submission estimated the total cost over the six-year period would be $90 million to < $100 million. The pre-PBAC response proposed a lower price for cabozantinib but did not provide updated financial estimates to reflect this.

6.116 The ESC and the evaluation noted the following points regarding the submission's financial estimates:

- The proportion of patients expected to receive third line and fourth line treatment for pNET and epNET was uncertain, as these proportions (24% third line and 14% fourth line) were based on retrospective chart reviews for seven tertiary care centres in the US; Dasari 2019 (Lung NET; three centres; n=83) and Kulke 2019 (GI NET; four centres; n=273). The generalisability of these studies to Australian clinical practice was unclear, and as such it was difficult to discern whether the assumed third line and fourth line treatment eligibility was a reasonable estimate for the target PBS population. The PBAC considered that, in the absence of alternative data, there estimates were likely reasonable;
- The flat uptake rate of [redacted]%, commencing in Year 1, for third line initiation therapy in the pNET population was likely overestimated as sunitinib and everolimus are established PBS listed therapies for pNET patients and per the requested restriction, pNET patients would be able to access cabozantinib following sunitinib or everolimus, but not vice versa. Therefore, it was uncertain to what degree patients and clinicians would opt for cabozantinib as third line treatment (if at all), as this reduces the number of treatment options later line. Overall, the ESC considered that uptake rates and utilisation in the third-line versus fourth-line settings were difficult to predict. The PBAC agreed with the ESC that uptake rates were difficult to predict and advised that the ratio of patients initiating cabozantinib in the financial estimates should be around [redacted]% in third line versus around [redacted]% in fourth line, consistent with the calculation of the weighted price (refer to the next dot point);
- The evaluation considered that the flat uptake rate of [redacted]%, commencing year 1, for third line initiation therapy in the epNET population may be underestimated as cabozantinib would be the only protein kinase inhibitor available for epNET. Conversely, the evaluation also considered that the uptake rate for fourth line initiation therapy (especially in incident patients) for epNET was likely overestimated, as epNET patients would be expected to receive cabozantinib in third line. On the other hand, the PBAC considered that the fourth line cohort may also receive treatment in fifth and subsequent lines and therefore the uptake rate in the fourth line cohort should be high, particularly given the absence of alternative treatment options in this setting. Overall, the PBAC considered that utilisation of cabozantinib was likely to be more common in the fourth (and later) lines compared with third line, and that the ratio of patients initiating cabozantinib in the financial estimates should be around [redacted]% of initiating patients being in third line versus around [redacted]% in fourth line, consistent with the calculation of the weighted price (refer to

paragraph 7.12). Thus, the PBAC advised that the uptake rates would need to be adjusted to reflect this;

- The assumed compliance for cabozantinib was uncertain, as the 'percentage of doses held' of 7.7% in pNET and 10.8% in epNET could not be independently verified from the CSR. However, this was consistent with the submission's economic model, where the RDI was not applied due to the flat pricing structure requested by the submission. i.e. a flat price was requested across all strengths of cabozantinib tablets; and
- As discussed in paragraph 6.106, the chemotherapy treatment duration of 10 months (which informed the chemotherapy offsets in the third line setting in epNET) was uncertain. The PBAC considered the duration of chemotherapy in third line epNET (i.e. CAPTEM and FOLFOX) should be consistent with cabozantinib, per the assumptions advised for the CMA (i.e. 8.48 months).
- The submission's economic model also assumed that a proportion of epNET patients would receive chemotherapy post fourth line setting instead of at third line. Therefore, the evaluation considered that, for some patients, chemotherapy may be displaced to a later line of therapy (and therefore should not be included as an offset).

Financial Management – Risk Sharing Arrangements

6.117 The submission did not propose any risk-sharing arrangements for the requested listing of cabozantinib in NETs.

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

7 PBAC Outcome

7.1 The PBAC recommended cabozantinib for the treatment of patients with unresectable or metastatic, well-differentiated extra-pancreatic (epNET) or pancreatic (pNET) neuroendocrine tumours who have progressed on at least one prior systemic therapy other than a somatostatin analogue (SSA). The PBAC considered that cabozantinib would provide an additional treatment option for patients with these relatively rare conditions where treatment options are limited. The PBAC was satisfied that cabozantinib provides for some patients an improvement versus best supportive care (BSC) in the 'fourth line' setting noting the benefits in progression free survival shown in the CABINET trial. The PBAC was also satisfied that, in the 'third line' setting, cabozantinib provides non-inferior effectiveness versus: sunitinib or everolimus in pNET; or chemotherapy in epNET. The PBAC's recommendation for listing was based on, among other matters, its assessment that the overall cost-effectiveness of cabozantinib (across the various cost-utility analyses and cost-minimisation approaches presented) would be acceptable with a price reduction using revised parameters to inform the economic evaluations. The PBAC also considered that

revisions were required to the assumptions across the proposed treatment settings informing the weighted price.

7.2 The PBAC welcomed advice from consumers, clinicians and organisations (via the consumer comments and the sponsor hearing) that there is a clinical need for additional treatments for patients with NETs. The PBAC noted that NETs are relatively rare, indolent at onset and progress slowly, with a variable prognosis depending on location, stage and grade. The Committee noted that there are several therapies available for pNET including sunitinib or everolimus, chemotherapy, PRRT and also SSAs in patients who are somatostatin receptor positive. However, the PBAC noted that treatment options are more limited for patients with epNET, particularly for patients who are not somatostatin receptor positive and for patients in whom chemotherapy can be challenging.

7.3 The PBAC noted that the comparators proposed in the submission were:

- in the fourth line setting, BSC for patients with pNET or epNET; and
- in the third line setting, sunitinib and everolimus for patients with pNET, and chemotherapy (FOLFOX and CAPTEM) for patients with epNET.

The PBAC considered that the lines of therapy are not clear-cut given the variable presentation and course of the disease and the heterogeneity in patient and tumour characteristics, which impacts clinical suitability for each therapy. The pre-PBAC response stated that the approach taken in the submission could be considered to represent a mixed comparator rather than strict lines of therapy. Overall, in the context of a rare condition, the PBAC considered the comparators nominated by the submission were reasonable.

Clinical evidence

7.4 The PBAC noted the submission was based on the randomised, placebo-controlled CABINET trial, which evaluated the efficacy and safety of cabozantinib in patients with pNET or epNET, whose disease had progressed after at least one prior FDA-approved therapy (everolimus, sunitinib or Lu-177 DOTATATE, a form of PRRT). The CABINET trial directly informed the efficacy of cabozantinib versus BSC in the fourth line setting, and was used to inform indirect comparisons in the third line setting.

7.5 The PBAC considered that the submission's claim of superior comparative effectiveness versus BSC in the fourth line setting in pNET and epNET was reasonable based on the PFS results of the CABINET trial. The PBAC noted that a statistically significant PFS benefit was observed with a hazard ratio (HR) of 0.38 (95% confidence interval (CI): 0.25, 0.58) reported for epNET, and a HR of 0.23 (95% CI: 0.12, 0.42) for pNET (based on blinded independent central review).

7.6 However, the PBAC noted that cabozantinib did not demonstrate a statistically significant benefit in overall survival versus BSC for epNET or pNET, even with

crossover adjustment (see Table 7). The Committee further noted that, as CABINET was terminated early, there was unlikely to be further informative data forthcoming in relation to overall survival.

7.7 The PBAC considered the evidence in the third line setting, which was based on indirect comparisons, was weak given the transitivity, applicability and quality issues with the included studies (refer to paragraphs 6.47 and 6.50). However, the Committee considered it was clinically plausible that cabozantinib would be associated with non-inferior effectiveness in the third line setting (versus sunitinib and everolimus in pNET, and chemotherapy in epNET).

7.8 The PBAC considered that cabozantinib was associated with inferior safety versus BSC in fourth line epNET and pNET, noting there were no new safety findings for cabozantinib in the CABINET trial.

7.9 The PBAC considered that the claim of a different but manageable safety profile in the third line setting (versus sunitinib and everolimus in pNET, and chemotherapy in epNET) was not well-justified and that the term "manageable" was not informative, but that a claim of non-inferior safety was likely reasonable.

Weighted price and economic evaluations

7.10 The PBAC noted that the submission presented four economic evaluations:

- in the fourth line setting, cost-utility analyses (CUA) versus BSC for patients with epNET or pNET; and
- in the third line setting, a cost-minimisation approach (CMA) versus chemotherapy for patients with epNET and a CMA versus sunitinib/everolimus for patients with pNET.

7.11 The submission proposed a single weighted price, based on indication-specific prices derived from the economic evaluations for the four requested populations, which were weighted by expected utilisation in each of the settings. The PBAC considered that a single flat price across the lines of therapy was reasonable, noting the difficulty in defining lines of therapy.

7.12 The PBAC considered the weightings of use across the different settings were difficult to predict, which was acknowledged by the clinician at the sponsor hearing. The submission assumed cabozantinib would be used more frequently in fourth line (the submission assumed: 74% and 26% use in 4L and 3L, respectively for pNET; and 64% and 36% use in 4L and 3L, respectively for epNET), based on proportions from the CABINET trial. However, the PBAC considered the applicability of these data were unclear in terms of informing this estimate (refer to paragraph 6.68), and agreed with the ESC that it did not seem plausible for there to be nearly three time more patients in the fourth line setting versus the third line setting in pNET. Overall, in the absence of reliable data, the PBAC considered that the ratio of use of cabozantinib should be [redacted]% use in third line versus [redacted]% use in fourth line (in both pNET and epNET).

7.13 Further, in terms of deriving the weighted price, the PBAC considered that the proportion of patients with pNET relative to epNET should account for the differential proportions of patients with stage IV disease between the two conditions, in line with the approach taken in the financial estimates of applying the proportions from White 2022 (refer to paragraph 6.71).

7.14 For the CUA in the fourth line setting, the PBAC noted the pre-PBAC response made the following changes to the economic model: the time horizon was reduced to 7.5 years (from 10 years); the half cycle correction was removed for drug costs; the proportion of patients receiving post-progression therapy was assumed to be the same in the cabozantinib and BSC arms; and Kaplan-Meier data were applied for 12 months (for OS, PFS and time on treatment). The PBAC considered these changes were appropriate, with the exception that Kaplan-Meier data should be applied for 24 months rather than 12 months to better reflect the available evidence, and to reduce the uncertainty with respect to the modelled gains for OS.

7.15 In terms of deriving a weighted price in the fourth line setting, the PBAC considered that an ICER of no higher than $55,000 to < $75,000 /QALY would be reasonable in epNET given the lack of alternative treatment options (refer to paragraph 7.2) and the rarity of the condition. Further, the PBAC considered that the price required to achieve this ICER should also be applied to the pNET setting (i.e. the indication-specific price should be the same in both pNET and epNET in the fourth line setting, similar to the approach applied in the submission), refer to paragraph 6.65 and Table 14. The PBAC noted this would result in an ICER of around $55,000 to < $75,000 /QALY in pNET, where more alternative treatment options are available (sunitinib and everolimus).

7.16 For the CMA versus chemotherapy in the third line epNET setting, the PBAC noted the submission assumed that 50% of patients would receive CAPTEM, and the other 50% would receive FOLFOX in the comparator arm. However, the PBAC considered that CAPTEM is more widely used than FOLFOX in clinical practice given the administration requirements of FOLFOX. Thus, the PBAC advised that, given the absence of reliable data, a ratio of 60% CAPTEM to 40% FOLFOX may be more reasonable in this setting. Further, the PBAC considered the CMA should assume the same treatment duration for chemotherapy (CAPTEM and FOLFOX) as applied for cabozantinib (i.e. 8.48 months).

7.17 The PBAC acknowledged that some of the parameters informing the CMAs and weighted price derivation were based on assumptions around utilisation of cabozantinib and chemotherapy in clinical practice and thus were associated with uncertainty (in particular the proportions of use of: cabozantinib in third versus fourth line; and CAPTEM versus FOLFOX in current clinical practice). However, the PBAC considered the result of the recommended scenario was reasonable given it reflected the clinical need and uncertainty in the available clinical evidence. The overall scenario recommended by the PBAC to determine the weighted price for cabozantinib in NETs is outlined in Table 14.

Financial estimates

7.18 In terms of the financial estimates, the PBAC considered the key uncertainties were the uptake rates and agreed with the ESC that these were difficult to predict. The PBAC advised that that the ratio of patients initiating cabozantinib in the financial estimates should be around [redacted]% in third line versus [redacted]% in fourth line, consistent with the derivation of the weighted price. Thus, the PBAC advised that the uptake rates would need to be adjusted to reflect this. Overall, the PBAC considered that the resulting financial impact to the PBS/RPBS should be no higher than outlined in Table 29.

7.19 The PBAC considered that there was a low risk of cabozantinib use outside the restriction and advised that a risk sharing arrangement would not be required.

Restriction

7.20 The PBAC noted that, at the time of consideration, the TGA Delegate had proposed to register cabozantinib, varying the requested indication from 'patients who have progressive disease while on prior treatment, or who are intolerant to prior treatment', to 'patients who had progressed on at least one prior systemic therapy other than a somatostatin analogue'. Based on the revised indication proposed by the TGA Delegate, the PBAC considered that the restriction should be revised to state that 'the patient must have progressed on at least one prior systemic therapy other than a SSA', noting that this would align more closely with the population enrolled in the CABINET trial.

7.21 In terms of the restriction, the PBAC advised that:

- the following clinical criterion requested in the submission: "the condition must be World Health Organization (WHO) grade 0, 1 or 2", was not required however the clinical criterion: "Patient must have a WHO performance status of 2 or less" should be included in the restriction; for consistency with the CABINET trial.
- cabozantinib use should be restricted to once per lifetime.
- the use of sunitinib or everolimus should not be permitted following progression on cabozantinib (in patients with pNET). Hence a prescribing instruction was added to both the initial and continuing treatment phase to explain this to prescribers.
- it would be reasonable for a treatment course to continue until progression, based on the RECIST criteria.
- the restriction should be age agnostic (i.e. remove the following criterion proposed by the submission: "Patient must be aged 18 years or older").

7.22 The PBAC considered that in the context of a rare condition, the clinical place for cabozantinib was instead of, or before, BSC in line with the evidence from the CABINET trial. Accordingly, the PBAC considered that use of sunitinib or everolimus should not be permitted following progression on cabozantinib (in patients with pNET). This

would require flow-on amendments to the existing restrictions for initiation of sunitinib and everolimus in pNET as outlined in the italics below:

- "Patients who have developed progressive disease *with any of: (i)* everolimus *(ii) cabozantinib* are not eligible to receive PBS-subsidised treatment with sunitinib for this condition"; and
- "Patients who have developed intolerance *with any of: (i)* everolimus *(ii) cabozantinib* of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised sunitinib."

Furthermore, the everolimus initiation restriction in the pNET setting would need to be amended per the italics:

- "Patients who have developed progressive disease *with any of: (i)* sunitinib *(ii) cabozantinib* are not eligible to receive PBS-subsidised everolimus *for this condition*"; and
- "Patients who have developed intolerance *with any of: (i)* sunitinib *(ii) cabozantinib* of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised everolimus."

7.23 The PBAC considered that the following treatment criteria should be removed from the listing requested in the submission: "The treatment must be the sole PBS-subsidised therapy for this condition" to enable use in combination with SSAs. This would be consistent with the CABINET trial in which 35 (55%) and 92 (69%) patients randomised to the cabozantinib arm in the pNET and epNET cohorts, respectively, received concurrent SSA therapy.

7.24 Correspondingly, the PBAC considered that the existing PBS listings for SSA therapies (octreotide and lanreotide) in non-functional gastroenteropancreatic neuroendocrine tumour (GEP-NET)) should be updated to allow concurrent use with cabozantinib. As such, the PBAC considered that the following criterion should be removed from the current octreotide and lanreotide listings: "The treatment must be the sole PBS-subsidised therapy for this condition" and replaced with "*The treatment must be: (i) as monotherapy; or (ii) in combination with cabozantinib".*

7.25 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 while clinically relevant improvements in progression-free survival were evident there was no statistically significant difference in overall survival;

b) The treatment is not expected to address a high and urgent unmet clinical need given the availability of other therapies;

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.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new restrictions as follows:

Initial treatment phase

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
CABOZANTINIB					
cabozantinib 60 mg tablet, 30	NEW	1	30	2	cabometyx
cabozantinib 40 mg tablet, 30	NEW	1	30	2	cabometyx
cabozantinib 20 mg tablet, 30	NEW	1	30	2	cabometyx

Restriction Summary [new1] / Treatment of Concept: [new1A]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]
Prescribing rule level	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Severity: Metastatic or unresectable
	Condition: Neuroendocrine tumour
	Indication: Metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET) or extra-pancreatic neuroendocrine tumour (epNET)
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must not have received prior PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) following at least one prior systemic therapy other than a somatostatin analogue for this indication prior to initiating treatment with this drug
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less prior to initiating treatment with this drug

	Treatment criteria:
	Patient must not be undergoing treatment with this drug more than once per lifetime
	Prescribing Instructions: Patients who develop disease progression while receiving PBS-subsidised treatment with cabozantinib for this condition are not eligible to receive subsequent PBS-subsidised treatment with any of: (i) sunitinib (ii) everolimus;
	Prescribing Instructions: Patients who develop intolerance while receiving PBS-subsidised treatment with cabozantinib are eligible to receive subsequent PBS-subsidised treatment with any of: (i) sunitinib (ii) everolimus
	Prescribing Instructions: Disease progression must be documented in the patient's medical records
	Administrative advice: Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.

Continuing treatment phase

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
CABOZANTINIB					
cabozantinib 60 mg tablet, 30	NEW	1	30	5	cabometyx
cabozantinib 40 mg tablet, 30	NEW	1	30	5	cabometyx
cabozantinib 20 mg tablet, 30	NEW	1	30	5	cabometyx

Restriction Summary [new2] / Treatment of Concept: [new2A]		
Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (Streamlined) [new/existing code]
Prescribing rule		**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
	7608	**Administrative Advice:** Special Pricing Arrangements apply.
		Severity: Metastatic or unresectable
		Condition: Neuroendocrine tumours
		Indication: Metastatic or unresectable, well-differentiated malignant pancreatic neuroendocrine tumour (pNET) or extra-pancreatic neuroendocrine tumour (epNET)
		Treatment Phase: Continuing treatment
		Clinical criteria:
		Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to (TBC – PBS listing date); OR
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition

	Prescribing Instructions A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
	Prescribing Instructions: Patients who develop disease progression while receiving PBS-subsidised treatment with cabozantinib for this condition are not eligible to receive subsequent PBS-subsidised treatment with any of: (i) sunitinib (ii) everolimus;
	Prescribing Instructions: Patients who develop intolerance while receiving PBS-subsidised treatment with cabozantinib are eligible to receive subsequent PBS-subsidised treatment with any of: (i) sunitinib (ii) everolimus:
	Treatment criteria:
	Patient must not be undergoing treatment with this drug more than once per lifetime

Flow on to Lanreotide (11531Y, 11527Q, 11736Q)

Remove Concept ID (7890/7889) and replace with the following:

	~~**Clinical criteria:**~~
	~~The treatment must be the sole PBS-subsidised therapy for this condition~~
	Clinical criteria:
	The treatment must be: (i) as monotherapy; or (ii) in combination with cabozantinib

Flow on to Octreotide (11893Y, 11894B and 11896D)

Remove Concept ID (7890/7889) and replace with the following:

	~~**Clinical criteria:**~~
	~~The treatment must be the sole PBS-subsidised therapy for this condition~~
	Clinical criteria:
	The treatment must be: (i) as monotherapy; or (ii) in combination with cabozantinib

Flow on to Everolimus (11377T, 11362B)

Amend Concept ID (12432) with the following:

	Prescribing Instruction: Patients who have developed progressive disease with any of: (i) sunitinib (ii) cabozantinib are not eligible to receive PBS-subsidised everolimus for this condition

Amend Concept ID (12433) with the following:

	Prescribing Instruction: Patients who have developed intolerance with any of: (i) sunitinib (ii) cabozantinib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised everolimus.

Flow on to Sunitinib (10004M, 2959R, 2837H, 10464R)

Amend Concept ID (12467) with the following:

	Prescribing Instruction: Patients who have developed progressive disease with any of: (i) everolimus (ii) cabozantinib are not eligible to receive PBS-subsidised treatment with sunitinib for this condition

Amend Concept ID (12468) with the following:

	Prescribing Instruction: Patients who have developed intolerance with any of: (i) everolimus (ii) cabozantinib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised sunitinib

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.