



Draft Reimbursement Recommendation

Cabozantinib

Reimbursement request: For the treatment of adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have received at least 1 prior therapy

Requester: Public drug programs

Draft recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Cabozantinib?

The Formulary Management Expert Committee (FMEC) recommends that cabozantinib be reimbursed for adult patients with locally advanced or metastatic extra-pancreatic or pancreatic tumours who have received at least one prior therapy, provided certain conditions are met.

What Are the Conditions for Reimbursement?

Cabozantinib may be initiated in patients for the treatment of metastatic extra-pancreatic or pancreatic neuroendocrine tumours if the following conditions are met: the tumour grade is consistent with WHO tumour grade 1 to 3, there is histological documentation of neuroendocrine tumour of pancreatic, gastrointestinal, lung, thymus other or unknown primary site, there is disease progression or unacceptable side effects after at least one prior therapy other than somatostatin analogue and there is good performance status. A price reduction for cabozantinib may be required.

Why Did CDA-AMC Make This Recommendation?

FMEC reviewed the CDA-AMC report, which included a review of the clinical evidence, specifically the CABINET trial and a cost comparison of cabozantinib versus other treatments used in Canada. Cabozantinib improved progression-free survival compared to placebo. FMEC also considered input received from 1 patient group from the Canadian Neuroendocrine Tumour Society (CNETS) and 1 clinician group from the Commonwealth Neuroendocrine Tumour Society (CommNETS).

Based on the CDA-AMC assessment of the health economic evidence, which consisted of a cost comparison table, reimbursement of cabozantinib is associated with higher drug acquisition costs to publicly funded drug programs than best supportive care, everolimus, sunitinib, and capecitabine in combination with temozolomide based on publicly available list prices; cabozantinib is associated with lower drug acquisition costs to publicly funded drug programs than Lu-177. The cost-effectiveness of cabozantinib compared to relevant comparators is unknown. A price reduction may therefore be required.

FMEC concluded that cabozantinib demonstrates acceptable clinical value. FMEC also considered unmet clinical needs, distinct social and ethical considerations, economic considerations, and impact on health systems.

Therapeutic Landscape

What Is Neuroendocrine Tumour?

Neuroendocrine tumours (NETs), including extra-pancreatic (epNETs) and pancreatic (pNETs) types, originate from secretory cells and can occur in various organs. These tumours can be functional, causing various symptoms, or nonfunctional, presenting with nonspecific symptoms and leading to delays in diagnosis. These tumors significantly impact individuals' quality of life and functional performance. In Canada, an Ontario-based study (2015) reported an increase in incidence from 2.46 per 100,000 to 5.86 per 100,000 over 15 years, with pNETs accounting for about 10% of cases. The estimated overall survival (OS) rates for patients with NETs are 68.3% at 3 years, 61.0% at 5 years, and 46.5% at 10 years.

What Are the Current Treatment Options?

For locally advanced or metastatic epNET or pNET, treatment approaches vary based on tumour grade, differentiation, functionality, and the extent and location of the disease. For localized solid tumours, surgery is typically the first-line treatment. For patients with metastatic disease, systemic drug therapies are used. Somatostatin analogues (SSAs) are generally the initial therapy for patients with unresectable metastatic disease or hormonal overproduction syndromes. For those who have progressed while on SSAs, treatment options include targeted agents like everolimus, sunitinib and cabozantinib, chemotherapy such as capecitabine plus temozolomide (CAPTEM), Lu-177 dotatate (Peptide Receptor Radionuclide Therapy [PRRT]).

What Is the Treatment Under Review?

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases, which are involved in tumour cell proliferation and angiogenesis. Cabozantinib is approved by Health Canada for the following indications: renal cell carcinoma, hepatocellular carcinoma and differentiated thyroid carcinoma. This review of cabozantinib is for off-label use in neuroendocrine tumours. Cabozantinib is available as an oral tablet in doses of 60mg, 40mg, or 20mg.

Why Did We Conduct This Review?

As identified by clinicians, cabozantinib offers a novel mechanism of action and potential to fulfil an unmet need in adult patients with locally advanced or metastatic epNET or pNET. Given the active pharmaceutical ingredient (API) patent of cabozantinib has expired, this drug is eligible for a nonsponsored reimbursement review, per the [Procedures for Reimbursement Reviews](#). Of note, cabozantinib has two generics under review by Health Canada.


At the request~~ed~~ from the public drug programs, we initiated a review to inform a recommendation on whether cabozantinib should be reimbursed for adults with locally advanced or metastatic epNET or pNET who have received at least 1 prior therapy.

Input From Interested Parties

- **Canadian Neuroendocrine Tumour Society (CNETS)** as a patient group provided input summarizing patient experiences and perspectives on living with NETs, drawing from multiple sources including the Global NET Patient Survey (2017), the NET Patient Experiences and Perspectives Survey (2022), and qualitative interviews with patients and caregivers who have experience with cabozantinib. Patients reported that NETs significantly reduce quality of life (QoL), with symptoms such as fatigue, diarrhea, and pain, which affect daily activities, emotional well-being, social interactions, and the ability to work.
- **Commonwealth Neuroendocrine Tumour Society (CommNETS)** as a clinician group noted that NETs are among the fastest-growing classes of cancers in Canada and globally. Treatment goals for patients with locally advanced or metastatic epNET or pNET include prolonging survival, delaying disease progression, managing symptoms, preventing treatment-related complications, and maintaining or improving QoL and functional status. Available systemic treatment options include SSAs, targeted agents, PRRT, and other chemotherapy when appropriate.

► Refer to the main report and the supplemental material document for this [review](#).

Person With Lived Experience



A Person with Lived Experience from Manitoba with Stage 4 neuroendocrine cancer shared her treatment journey with FMEC. After limited options early in her diagnosis and multiple radiation therapies, she accessed PRRT in Quebec in 2021—traveling from Manitoba to Quebec City six times. While treatment and flights were covered, she needed to pay for accommodations and meals, and spend time away from home. She later began cabozantinib through a compassionate access program. She appreciated oral therapy for maintaining quality of life, despite initial side effects like fatigue, hair loss, and muscle spasms. Dose adjustments and monitoring led to symptom relief and reduced tumor activity. Her latest PET Scan showed no new tumor growth, which she called an incredible gift. She emphasized the need for equitable access to this therapy, noting its ease of use and effectiveness compared to other options with harsher side effects and a poor quality of life.

Disclaimer: The perspectives shared by people with lived experience who present to the committee reflect their individual experiences and are not necessarily representative of all people with the same condition or course of treatment. Their insights provide valuable context about what a patient, support person or caregiver might go through when facing this condition or treatment, helping to inform the committee’s deliberations. These narratives complement other forms of evidence and input and should be considered as part of a broader understanding of the condition and treatment under review. Where gender or gendered pronouns are used in these narratives, they are included with the permission of the individual.

Summary of Deliberation

FMEC deliberated on all domains of value of the deliberative framework prior to developing their recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, please refer to the [Expert Committee Deliberation at Canada's Drug Agency](#) document.

FMEC considered the following key discussion points, organized by the five domains of value.



Clinical Value

- **FMEC concluded that cabozantinib demonstrates acceptable clinical value versus appropriate comparators in the Canadian setting.**
- Through reflection on the input from one patient group or insights shared by the person with lived experience, FMEC members noted the following important patient values or perspectives: patients value progression free survival as an outcome. However, patients also value symptom control and would like to see more treatment options available to address drug resistance and to improve their overall outcomes and the quality of life.
- **FMEC** members highlighted the following discussion points:
 - FMEC noted that neuroendocrine tumours encompass many different types of cancers with both endocrine and neural characteristics. Depending on the tumours' site(s), the treatment options and management can be variable. However, guest specialists have shared that most patients would begin with a treatment with a somatostatin analog (SSA) which has both antiproliferative properties and the ability to manage symptoms related to secretory tumours.. As per the guest specialists, most patients would typically remain on a SSA, while additional treatments are needed when there is disease progression. FMEC noted there is some variation of practice in terms of how long patients remain on SSAs.
 - In the CABINET study where cabozantinib was compared to placebo, cabozantinib was associated with a HR of 0.38 (95% CI, 0.25 to 0.59) for disease progression or death in the extrapancreatic neuroendocrine tumour (epNET) cohort and a HR of 0.23 (95% CI, 0.12 to 0.42) in the pancreatic neuroendocrine (pNET) cohort. Nearly all participants had received prior SSA therapy, with most continuing SSAs as background treatment during the CABINET trial. FMEC noted that the progression free survival is an important outcome to patients and is overall satisfied with the level of evidence on this outcome.
 - FMEC also discussed the concern for potential toxicity with cabozantinib. In the CABINET study where cabozantinib was compared to placebo, patients in the cabozantinib had higher proportions of any grade treatment-related AEs, SAEs and WDAEs. In the epNET cohort, the most common (10% or more) treatment-related grade 3 or 4 adverse events were hypertension (21%), fatigue (13%) and diarrhea (11%). In the pNET cohort, the most common (10% or more) treatment-related grade 3 or 4 adverse events were hypertension (22%), fatigue (11%) and thromboembolic events (11%).
 - FMEC discussed whether cabozantinib was compared and assessed against an appropriate comparator which is placebo. FMEC discussed that cabozantinib may address the needs to delay progression in neuroendocrine tumours. However, there were some dissenting opinions on whether we need more treatment options in neuroendocrine tumours and whether the comparative evidence against placebo is clinically relevant. FMEC heard from the clinician experts that at the time of the CABINET trial was conducted, placebo as the comparator in the trial was a reasonable approach, given

that other treatment options were not funded or available at that time. Lu-177 dotatate, for example, was not standard of care at the time the trial was initiated. In essence, the trial evaluated cabozantinib as compared to the standard of care at the time, when no other treatments were funded or available. In the current Canadian context, for patients with lungNETS, who make up the highest proportion of neuroendocrine cancers, placebo (reflecting the standard of care) is an appropriate comparator, as everolimus is currently the only funded treatment available in first line for these patients. FMEC agreed with the guest specialists that for some patients, a placebo would be an appropriate comparator, especially if they had already exhausted multiple lines of therapy and had no other treatment options available.

- FMEC acknowledged that there is evidence to compare cabozantinib to placebo but there is a lack of comparative evidence with other treatment options available for neuroendocrine tumours. FMEC noted that given the trial design included NETs patients with variable and heterogeneous disease characteristics where treatment options are also variable, some patients such as those with lungNETS would have limited options in which case the use of a placebo as a comparator in the trial would be reasonable. However in patients with pNETs where there are more options including chemotherapies, sunitinib and everolimus, the comparative evidence between cabozantinib and these treatment options is lacking.



Unmet Clinical Need

- **FMEC concluded that there is significant clinical need arising from neuroendocrine tumours despite available treatments.**
- Through reflection on the input from one patient group or insights shared by the person with lived experience, FMEC members noted the following important patient values or perspectives: patients have noted that resistance to current therapies is concerning and that treatment options with intolerable side effects (e.g., everolimus) are problematic; patients are interested to have more effective and better tolerated treatment options for neuroendocrine tumours.
- **FMEC** members highlighted the following discussion points:
 - FMEC discussed and agreed that there are other treatment options available for patients with neuroendocrine tumours. These include somatostatin analogues (SSA), peptide receptor radionuclide therapy (PRRT) and other tyrosine kinase inhibitor (TKI). However, not all of these options are available or acceptable to patients.
 - FMEC also highlighted that neuroendocrine tumour is an incurable condition; patients are experiencing symptoms such as fatigue and diarrhea. These symptoms may affect their daily activities and emotional health.
 - FMEC also discussed that there are unmet needs related to the condition; these include the need to prolong survival, to delay progression, to reduce symptoms, to prevent treatment complications and to improve and maintain quality of life.
 - FMEC noted that neuroendocrine tumour is relatively rare; hence, there are challenges with evidence generation to support treatment in this therapeutic area.

- FMEC heard from the guest specialists who underscored the opportunity for patients with lungNETs, who make up the highest proportion of neuroendocrine cancers, as everolimus is currently the only funded treatment available in first line for these patients, cabozantinib if reimbursed would be the second drug approved for lungNETS. The guest specialists also shared concerns that everolimus is associated with unfavourable side effects such as profound hyperglycemia, pneumonitis, interstitial lung disease. Other commonly reported adverse effects include fatigue, stomatitis and leukopenia. As such, the guest specialists also indicated that cabozantinib will be preferred over everolimus if funded in this setting.



Distinct Social and Ethical Considerations

- **FMEC concluded that cabozantinib would potentially address a significant nonclinical need arising from neuroendocrine tumours despite available treatments. FMEC did not identify any important measures that should be implemented to ensure that the use of cabozantinib addresses relevant social and ethical implications.**
- Through reflection on the input from one patient group or insights shared by the person with lived experience, FMEC members noted the following important patient values or perspectives: patients value the oral route of treatment administration. This has important mental health benefits for both the patient and the family when the patient can remain at home to receive this treatment.
- **FMEC** members highlighted the following discussion points:
 - FMEC discussed that as an oral treatment, cabozantinib offers the benefits of receiving treatment at home, especially for patients who live far from a cancer treatment center.
 - One FMEC member noted that patients with lower social economic status and those in rural areas may be disadvantaged with this cancer and this oral treatment may help address these problems.



Economic Considerations

- **FMEC concluded that there are economic considerations that are important to address when implementing the reimbursement of cabozantinib.**
- FMEC members highlighted the following discussion points:
 - For patients who have no other treatment options available, the drug acquisition costs of cabozantinib per patient per 28 days are higher than best supportive care.
 - The committee noted there are potentially relevant comparators for patients with NETs who have not yet exhausted multiple lines of therapy. These comparators include everolimus, sunitinib, capecitabine in combination with temozolomide, and Lu-177 dotatate.

- The drug acquisition costs per patient per 28 days of cabozantinib are higher than those of everolimus, sunitinib, and capecitabine in combination with temozolomide, and lower than those of Lu-177 dotatate.
- The comparative effectiveness relative to any of the active comparators is unknown, due to lack of data. Existing evidence from a randomized study comparing cabozantinib against placebo demonstrated meaningful PFS benefit.
- No Canadian cost-effectiveness or cost-utility studies were available.
- There is no evidence of clinical effectiveness against active comparators to justify a greater cost for cabozantinib relative to current treatments for this population.
- Two generic formulations are under review with Health Canada. Currently, only a branded version of cabozantinib (Cabometyx) is available in Canada.
- Cabozantinib is expected to have similar treatment related healthcare resource use as other treatments, except for Lu-177 dotatate, which has administration costs due to specialized infrastructure needs.
- Given the incremental costs and potential clinical benefit of cabozantinib specially for patients with no other treatments available, a price reduction may be warranted.

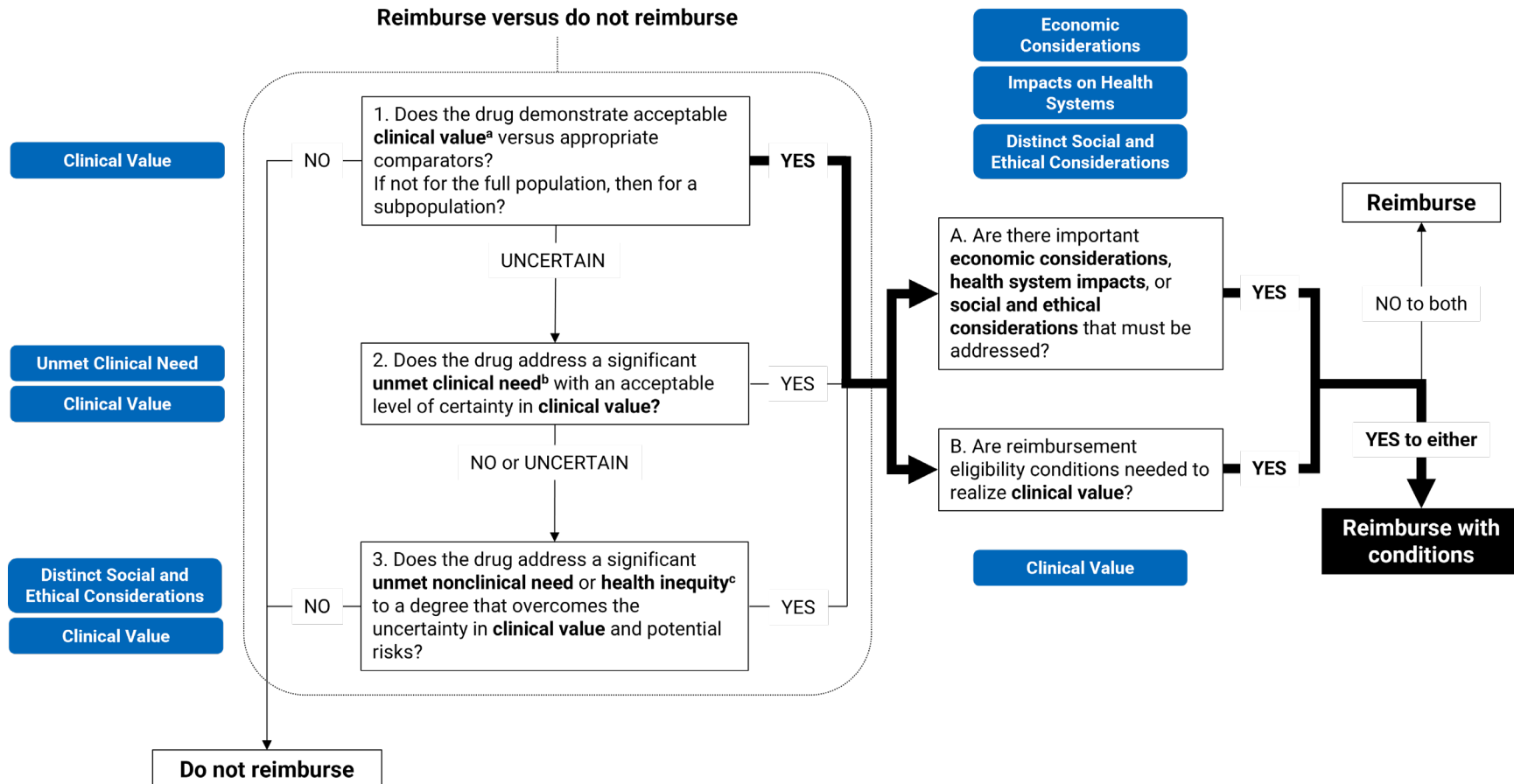


Impacts on Health Systems

- **FMEC did not identify any impacts on health systems that are important to address when implementing cabozantinib.**
- FMEC members highlighted the following discussion points:
 - FMEC discussed and agreed that there are no impacts on the health care system that need to be addressed to implement cabozantinib.
 - FMEC highlighted that the cost of oral medications is variable across jurisdictions and presents a concern for inequity. These treatments should be available for all patients regardless of where they reside within Canada.

Figure 1: Recommendation Pathway

Alt-text: Flow chart indicating the steps used by the committee for this recommendation. The committee determined that the drug demonstrates acceptable clinical value versus relevant comparators. Therefore, the committee recommended reimbursement of the drug for the patient population under consideration. After deliberating on economic considerations, impacts on health systems, distinct social and ethical considerations, and whether reimbursement conditions are needed to realize clinical value, the committee determined that reimbursement of the drug should be contingent upon 1 or more conditions being satisfied.



^a Acceptable clinical value refers to at least comparable clinical value (if the drug is expected to be substitutive treatment) or added clinical value (if the drug is expected to be additive treatment) versus appropriate comparators.

^b Significant unmet clinical need depends on all of the following: severity of the condition, availability of effective treatments, and challenges in evidence generation due to rarity of the condition or ethical issues.

^c Unmet nonclinical need and health inequity are key components within the distinct and social ethical considerations domain of value.

Full Recommendation

With a vote of 7 to 0, FMEC recommends that cabozantinib, for the treatment of adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours, be reimbursed if the conditions presented in [Table 1](#) are met.

Table 1: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Cabozantinib may be initiated in patients for the treatment of metastatic extra-pancreatic or pancreatic neuroendocrine tumours if the following conditions are met: 1.1. the tumour grade is consistent with WHO tumour grades 1 to 3, 1.2. there is histological documentation of neuroendocrine tumour of pancreatic, gastrointestinal, lung, thymus, other or unknown primary site, 1.3. there is disease progression or unacceptable side effects after at least one prior therapy other than a somatostatin analogue (SSA), and 1.4. there is good performance status.	There is evidence from the CABINET trial that cabozantinib improved progression-free survival when compared to placebo in adults with locally advanced or metastatic extra-pancreatic or pancreatic neuroendocrine tumours who have at least 1 prior therapy, not including SSAs.	-
Discontinuation and renewal		
2. Cabozantinib should be discontinued if there is any of the following: 2.1. disease progression 2.2. unacceptable toxicities	Consistent with clinical practice, patients in the CABINET trial discontinued treatment upon disease progression or treatment intolerance.	-
Prescribing		
3. Prescribing should be limited to clinicians with expertise in the diagnosis and management of neuroendocrine tumours.	This will ensure that appropriate treatment is prescribed for patients, and adverse events are optimally managed.	In CABINET trial, cabozantinib was prescribed as a single-drug regimen.
Pricing		
4. A price reduction may be required	Based on publicly available pricing information, cabozantinib is more costly than best supportive care and other active comparators, leading to incremental costs to the health care system. The cost-effectiveness of cabozantinib relative to best supportive care and other active comparators is currently unknown, thus, a price reduction may be required.	-

BSC = best supportive care; SOC = standard of care

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik. Two guest specialists from Ontario and the Prairies participated in this review.

Meeting date: July 17, 2025

Regrets: One expert committee member did not attend the meeting.

Conflicts of interest: None

Special thanks: Canada's Drug Agency (CDA-AMC) extends our special thanks to the individuals who presented directly to FMEC and to patient organizations representing the community of those living with NETs, particularly the Canadian Neuroendocrine Tumour Society, which includes Jackie Herman & Patricia Graefer.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.



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