Regimen Monograph

A - Regimen Name

CABO Regimen

Cabozantinib (Tablet)

Disease Site

Endocrine
Thyroid

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma who are not eligible for radioactive iodine therapy (RAI) or did not respond to prior RAI, and had disease progression following prior VEGFR-targeted therapy

Supplementary Public Funding

cabozantinib (tablet)
Exceptional Access Program (cabozantinib - For the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible) (EAP Website)

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B - Drug Regimen

cabozantinib (tablet)	60 mg	PO	Daily

Cabozantinib tablets and capsules are **not interchangeable**.

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate – Consider prophylaxis daily

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Prior to initiating cabozantinib therapy:

- Blood pressure should be well-controlled.
- Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected.
- Optimal control of thyroid function is recommended.
- An oral examination is recommended.

Hold treatment for at least 28 days prior to scheduled surgery, including dental surgery; resume based on clinical judgment of adequate wound healing.

Dosage with toxicity

Dose Levels

Dose Level	Cabozantinib (Tablet) Dose (mg/day)
0	60
-1	40
-2*	20
-3	Discontinue

*If previously receiving lowest dose, restart at the same dose if tolerated. Otherwise, discontinue.

Toxicity	Severity	Action
Palmar-Plantar Erythrodysesthesia	Intolerable Grade 2 or Grade 3	Hold**; restart at 1 dose level ↓
Hypertension	Intolerable Grade 2 OR Grade 3	Hold**, restart at 1 dose level ↓
	Grade 4 (including hypertensive crisis) OR Severe uncontrolled hypertension despite optimal therapy	Discontinue
Proteinuria	Grade 2 or 3	Hold**, restart at 1 dose level ↓
	Grade 4 (including nephrotic syndrome)	Discontinue
Osteonecrosis of the jaw (ONJ)	Any	Hold until complete resolution. Restart at 1 dose level ↓

Unmanageable fistula or GI perforation	Any	Discontinue
Severe hemorrhage		
Arterial or venous thromboembolic event that requires medical intervention (e.g., MI, cerebral infarction)		
Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia		
Posterior reversible leukoencephalopathy syndrome (PRES)		
Wound healing complications requiring medical intervention		
Other related hematologic/ non-hematologic/ organ toxicity	Intolerable grade 2 and cannot be adequately managed	Hold**; restart at 1 dose level ↓^
	≥ Grade 3#	

**Restart if toxicity resolved to ≤ grade 1 or baseline. Discontinue if toxicity does not resolve after 6 weeks.

#Including diarrhea that cannot be managed with standard antidiarrheal treatments.

^Or consider discontinuing for persistent or recurrent significant GI toxicity.

Hepatic Impairment

Liver Impairment	Cabozantinib (Tablet) Starting Dose (mg/day)
Mild (Child-Pugh class A)	No dosage adjustment required. Monitor patient closely.
Moderate (Child-Pugh class B)	40 mg. Monitor patient closely.
Severe (Child-Pugh class C)	Not recommended (has not been studied)

Renal Impairment

Renal Impairment	Cabozantinib (Tablet) Dose (mg/day)
Mild or moderate (eGFR ≥ 30mL/min)	No dosage adjustment required.
Severe (eGFR <29 mL/min)	Not recommended (has not been studied)

Dosage in the Elderly

No dosage adjustment is required. There were no overall differences in safety or efficacy between patients aged 65 or older and younger patients.

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F - Adverse Effects

Refer to cabozantinib (tablet) drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea (may be severe) • Fatigue • Nausea, vomiting	• Anorexia, weight loss • Hypertension (may be severe) • PPES • ↑ LFTs (may be severe) • Constipation	• Dysgeusia • Rash, dry skin • Abdominal pain • Abnormal electrolytes (↓ PO4, Mg, Ca, Na, K) • Mucositis • Hypothyroidism • Dysphonia • Cough, dyspnea • Anemia • Musculoskeletal pain	• Arterial / venous thromboembolism • Artery aneurysm / dissection • QT/PR prolongation • Hemorrhage • Wound complications • GI fistula/ perforation • Cholestasis • Hepatotoxicity • Hepatic

		• Dyspepsia • Proteinuria • Thrombocytopenia • Dizziness • Headache	encephalopathy • Pancreatitis • Osteonecrosis of jaw • PRES • Seizure • Pleural effusion

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G - Interactions

Refer to cabozantinib (tablet) drug monograph(s) for additional details

Cabozantinib is primarily metabolized by CYP3A4 and is susceptible to inhibitors and inducers of this isoenzyme.

- Consider alternatives to strong CYP3A4 inhibitors. If concurrent use with a strong inhibitor cannot be avoided, reduce cabozantinib dose by 20 mg. 2 to 3 days after discontinuation of the strong inhibitor, resume cabozantinib at previous dose.
- Avoid chronic co-administration with strong CYP3A4 inducers. If concurrent use cannot be avoided, increase cabozantinib dose by 20 mg as tolerated. 2 to 3 days after discontinuation of the strong inducers, resume cabozantinib at previous dose. Do not exceed a daily dose of 80 mg.
- Avoid co-administration to the extent possible with drugs that decrease heart rate or prolong QT/PR interval as concurrent use may increase the risk of life-threatening arrhythmias and bradycardia.

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H - Drug Administration and Special Precautions

Refer to cabozantinib (tablet) drug monograph(s) for additional details

Administration

- Tablets should be administered on an empty stomach, at least 1 hour before or at least 2 hours after food.
- Tablets should be swallowed whole, not chewed or crushed.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, an additional dose should not be taken within 12 hours of the next dose.
- Cabozantinib should be stored between 15^{o}C to 25^{o}C

Contraindications

- Patients who have a hypersensitivity to this drug or to any components of the formulation.

Other Warnings / Precautions:

- Patients with a history of severe bleeding should be evaluated carefully before starting treatment. Do not give cabozantinib to patients with or at risk for severe hemorrhage or a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.
- Patients with cardiac impairment were excluded from clinical studies.
- Use cabozantinib with caution in patients at risk for, or who have a history of:
    - Venous and/or arterial thromboembolism
    - Hypertension
    - Inflammatory bowel disease, tumour infiltration in the GI tract, or complications from prior GI surgery (particularly when associated with delayed or incomplete healing)
    - Severe bleeding
    - Low heart rate at baseline (< 60 beats per minute).
    - Syncope/arrhythmia, QT prolongation, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure
    - Wound complications

- Tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Use caution when driving or operating machinery as cabozantinib may cause fatigues, dizziness and weakness.

Pregnancy and Lactation:

- Cabozantinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- The effect of cabozantinib on oral contraceptives has not been studied; an additional contraceptive method (e.g. barrier) is recommended.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Probable. Documented in animals

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- ECG, heart rate and blood pressure; Baseline and as clinically indicated
- Electrolytes, including calcium, potassium and magnesium; Baseline and as clinically indicated, especially in patients at risk of severe arrhythmias
- Liver function tests; Baseline and as clinically indicated
- Renal function tests; Baseline and as clinically indicated
- Thyroid function tests; Baseline and as clinically indicated
- Clinical toxicity assessment for GI effects (including perforations, fistulas), bleeding, skin effects including PPES, respiratory and neurologic effects, thromboembolism, proteinuria, pancreatitis, osteonecrosis of the jaw and wound healing complications; At each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- INR for patients receiving warfarin; Baseline and as clinically indicated

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K - References

Brose MS, Robinson BG, Sherman SI, et al. Cabozantinib for previously treated radioiodine-refractory differentiated thyroid cancer: Updated results from the phase 3 COSMIC-311 trial. Cancer 2022 Dec 15;128(24):4203-12.

Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2021 Aug;22(8):1126-38.

Cabozantinib Drug Monograph, Ontario Health (Cancer Care Ontario).

CADTH reimbursement recommendation: cabozantinib (For the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma). November 2022.

March 2024 new ST-QBP regimen

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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