Regimen Monograph

A - Regimen Name

CABO Regimen

Cabozantinib (Tablet)

Disease Site

Gastrointestinal
Hepatobiliary / Liver / Bile Duct

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

Second-line treatment for advanced, unresectable hepatocellular carcinoma (HCC). Patients must have progressed on treatment with sorafenib or lenvatinib for HCC and have good performance status (ECOG ≤1) and liver function (Child-Pugh Class A). Refer to EAP criteria.

Supplementary Public Funding

cabozantinib (tablet)
Exceptional Access Program (cabozantinib - For the treatment of unresectable, advanced hepatocellular carcinoma (HCC), based on criteria) (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

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

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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 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
Hand-foot syndrome	Intolerable Grade 2 or Grade 3	Hold**; restart at 1 dose level ↓
Diarrhea	Intolerable Grade 2 OR Grade 3-4 diarrhea that cannot be managed with standard antidiarrheals	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.

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

Suggested Dose Modifications for Hepatic Toxicity During Treatment*:

Baseline		During treatment	Action
AST, ALT and bilirubin ≤ 3 x ULN	and	AST or ALT > 5 x ULN OR bilirubin > 3 x ULN	Consider hold, then • Reduce dose when resolved, OR • Discontinue if no recovery
Any	and	Drug-induced liver injury (AST or ALT > 3 ULN AND bilirubin > 2 x ULN in absence of another likely cause)	Discontinue

*adapted from Abou-Alfa et al, and Choueiri et al.

Hepatic Impairment

The clinical trial (Abou-Alfa et al) included patients with Child-Pugh class A, with AST/ALT < 5 x ULN at baseline.

Liver Impairment	Cabozantinib (Tablet) Starting Dose (mg/day)
Mild	No dosage adjustment required. Monitor patient closely.
Moderate	40 mg. Monitor patient closely.
Severe	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. Use with caution.
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) • HFS • ↑ 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 • Dyspepsia • Proteinuria • Thrombocytopenia • Dizziness • Headache	• Arterial / venous thromboembolism • Artery aneurysm / dissection • QT/PR prolongation • Hemorrhage • Wound complications • GI fistula/ perforation • Cholestasis • Hepatotoxicity • Hepatic encephalopathy • Pancreatitis • Osteonecrosis of jaw • PRES • Seizure • Pleural effusion • Vanishing bile duct syndrome (in patients with prior ICI treatment)

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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, it 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 were excluded from clinical studies if they had conditions such as cardiac impairment, untreated or incompletely treated varices with bleeding or high risk for bleeding.
- 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:

- This regimen 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

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

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 (more frequent monitoring may be required in patients at risk of serious arrhythmias or hypocalcemia)
- 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 hand-foot syndrome, 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

Abou-Alfa GK, Meyer T, Cheng AL. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63. DOI: 10.1056/NEJMoa1717002

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

Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1814-23.

December 2024 Updated Dose Modifications, Adverse effects, Warnings/Precautions, and Clinical Monitoring sections

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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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