Drug Monograph

A - Drug Name

cabozantinib (tablet)

COMMON TRADE NAME(S): Cabometyx®

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B - Mechanism of Action and Pharmacokinetics

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases (RTKs) including AXL, FLT3, KIT, MER, MET, RET, ROS1, TIE-2, TRKB, TYRO3, and VEGF, with effects on cell proliferation and angiogenesis.

Absorption	Effects with food	Co-administration with a high-fat meal increased peak concentrations by 41% and AUC by 57%, relative to fasted conditions.
	Peak plasma levels	3 to 4 hours
	Time to reach steady state	15 Days
Distribution	PPB	≥99.7% to plasma proteins
Metabolism	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Half-life	~ 99 hours
	Feces	54%

	Urine	27%

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C - Indications and Status

Health Canada Approvals:

- Renal cell carcinoma (RCC)
- Hepatocellular carcinoma (HCC)

Refer to the product monograph for a full list of approved indications.

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D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

The following table lists adverse effects that occurred in ≥10% of patients with advanced renal cell carcinoma receiving cabozantinib, where incidences were higher compared to everolimus in a phase III trial. Severe adverse events from other studies or post-marketing may also be included. Adverse effects marked with "^" were observed in combination treatment with nivolumab.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (1%)	E
	Artery aneurysm (rare)	E D L
	Artery dissection (rare)	E D L
	Hypertension (39%) (16% severe; including hypertensive crisis)	E
	PR interval prolonged ,bradycardia (rare)	E
	QT interval prolonged (rare)	E
	Venous thromboembolism (9%)	E D
Dermatological	Dry skin (11%)	E
	Palmar-plantar erythrodysesthesia syndrome (PPES) (42%) (8% severe)	E
	Rash (23%)	E

Gastrointestinal	Abdominal pain (23%)	
	Anorexia, weight loss (46%)	E
	Constipation (25%)	E
	Diarrhea (74%) (11% severe)	E
	Dyspepsia (12%)	E
	Gastrointestinal fistula (1%) (may be severe)	E
	GI perforation (1%)	E
	Mucositis (22%)	E
	Nausea, vomiting (50%) (4% severe)	E
General	Fatigue (56%) (9% severe)	E
	Wound complication (<2%) (may be severe)	E
Hematological	Anemia (17%)	E
	Hemorrhage (3%) (severe)	E
	Thrombocytopenia (11%)	E
Hepatobiliary	Cholestasis (<2%)	E
	Hepatotoxicity (rare)	E
	↑ LFTs (26%) (3% severe)	E
	Other - hepatic encephalopathy (4%)	E
	Pancreatitis (<2%)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (23%) (↓ PO4, Mg, Ca, Na, K)	E
	Adrenal insufficiency (5%) ^	E D
	Hyperthyroidism (10%) ^	E
	Hypothyroidism (21%)	E
Musculoskeletal	Musculoskeletal pain (14%) (including muscle spasms)	E
	Osteonecrosis of jaw (<2%)	D
Nervous System	Dizziness (11%)	E
	Dysgeusia (24%)	E
	Headache (11%)	E
	Posterior reversible leukoencephalopathy syndrome (PRES)	E
	Seizure (<2%)	E
Renal	Proteinuria (12%)	E
Respiratory	Cough, dyspnea (19%)	E
	Dysphonia (20%)	E

	Pleural effusion (may be severe)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for cabozantinib include diarrhea, fatigue, nausea, vomiting, anorexia, weight loss, hypertension, palmar-plantar erythrodysesthesia syndrome (PPES), ↑ LFTs, constipation, dysgeusia and abdominal pain.

Most side effects can occur early in the course of treatment, physicians should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Some side effects with early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES and GI events.

Cabozantinib is associated with an increased risk of **arterial or venous thrombotic events**, including fatal cases. In the HCC study, portal vein thrombosis was observed. Patients with a history of portal vein invasion appear to be at higher risk.

Serious **GI perforations and fistulas**, sometimes fatal, have been observed with cabozantinib. Persistent or recurring **diarrhea** while on treatment may be a risk factor for the development of anal fistula.

Severe cases of **artery dissection** (with or without hypertension) and **artery aneurysm** (including rupture) have been reported in patients using VEGFR TKIs.

Severe hemorrhage, including fatal events have occurred with cabozantinib. Risk factors in advanced HCC may include tumour invasion of major blood vessels, underlying liver cirrhosis resulting in esophageal varices, portal hypertension, and thrombocytopenia.

Osteonecrosis of the jaw (ONJ) occurred rarely with cabozantinib. Patients should maintain proper oral hygiene practices. If possible, withhold therapy for at least 28 days prior to scheduled invasive dental procedures.

Posterior reversible leukoencephalopathy syndrome (PRES), has been rarely observed. This syndrome should be considered in any patient presenting with multiple symptoms, including seizures, headache, visual disturbances, confusion or altered mental function.

Wound complications have been reported with therapy. Treatment should be held for at least 28 days prior to scheduled surgery, with resumption of therapy dependent on judgment of adequate wound healing post-surgery.

Primary and secondary **adrenal insufficiency** have been reported in cabozantinib combination treatment with nivolumab. Majority of patients received hormone replacement therapy, including systemic corticosteroids and adrenal insufficiency resolving in approximately 1/4 of patients.

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E - Dosing

Refer to protocol by which the patient is being treated.

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

Adults:

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.

Monotherapy:

Oral: 60 mg Daily

In combination with nivolumab:

Refer to the product monograph for details.

Dosage with Toxicity:

Dose Levels

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

†Dose levels for combination therapy differ from dose levels listed in table. Refer to product monograph for details.

*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	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		
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.

Monotherapy (in HCC) - Suggested Dose Modifications for Hepatic Impairment During Treatment:

Baseline		During treatment	Action
AST, ALT and bilirubin ≤ 3 x ULN	and	AST/ 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/ALT > 3 ULN and bilirubin > 2 x ULN in absence of another likely cause)	Discontinue

Dosage with Hepatic Impairment:

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

Monotherapy*	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)

*Refer to the product monograph for information on combination therapy.

Dosage with Renal Impairment:

Monotherapy*	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)

*Refer to the product monograph for information on combination therapy.

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.

Dosage based on ethnicity:

There were no overall differences in PK based on race.

Children:

The safety and efficacy has not been established in the pediatric population.

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F - Administration Guidelines

- 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.
- In combination treatment, administer nivolumab first during the day, then cabozantinib on an empty stomach, preferably in the evening.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, additional dose should not be taken within 12 hours of the next dose.
- Cabozantinib should be stored between 15°C to 25°C

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G - Special Precautions

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.
- The following patients were excluded from clinical studies:
  - Patients with cardiac impairment
  - Patients receiving concomitant anticoagulation or antiplatelet agents or patients with untreated, or incompletely treated, varices with bleeding or high risk for bleeding (HCC study)
- 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 fatigue, dizziness and weakness.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: No
- Clastogenicity: No
- Teratogenicity: Documented in animals
- Embryotoxicity: Documented in animals
    - Cabozantinib is not recommended for use in pregnancy. At least 2 forms of adequate contraception should be used by both sexes during treatment, and for at least **4 months** after the last dose.
    - The effect of cabozantinib on oral contraceptives has not been studied; an additional contraceptive method (e.g. barrier) is recommended.
- Excretion into breast milk: Unknown
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for **4 months** after the last dose.
- Fertility effects: Probable
  Documented in animals.

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H - Interactions

Cabozantinib is a substrate of CYP3A4 and a moderate inhibitor of the multidrug efflux pump P-glycoprotein (P-gp).

In vitro, cabozantinib is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

No dose adjustment required for cabozantinib when it is used with gastric pH modifying agents (e.g. PPIs, H2 RAs, antacids).

The effect of cabozantinib on oral contraceptives has not been studied; an additional contraceptive method (e.g. barrier) is recommended.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ cabozantinib exposure (co-administration with ketoconazole increased AUC by 38%)	↓ metabolism and ↓ clearance of cabozantinib	Consider alternatives to strong 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.
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ cabozantinib exposure (co-administration with rifampicin decreased AUC by 77%)	↑ metabolism and ↑ clearance of cabozantinib	Avoid chronic co-administration with strong 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.
MRP2 Inhibitors (i.e. cyclosporine, reserpine, estradiol-17β-glucuronide, etc)	↑ cabozantinib concentration and/or toxicity	Cabozantinib is a substrate of MRP2	Caution; monitor therapy
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ substrate concentration and/or toxicity	Cabozantinib is a P-gp inhibitor	Caution; monitor therapy
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of life-threatening arrhythmias	Additive	Avoid co-administration to the extent possible.
Drugs that decrease heart rate and/or prolong PR	↑ risk of bradycardia and PR Interval	Additive	Avoid co-administration to the extent possible.

Interval (i.e. antiarrhythmics, beta antagonists, non-dihydropyridine Ca channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, HIV protease inhibitors, alpha2-adrenoceptor agonists, etc)			
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of life-threatening arrhythmias		Caution; monitor therapy
Drugs with high protein binding (e.g. warfarin)	Possible ↑ effects of displaced drugs	Cabozantinib protein binding may displace other protein-bound drugs	Caution; monitor therapy (e.g. INR)
Bisphosphonates	↑ risk of ONJ	Additive	Caution

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
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 serious arrhythmias

Liver function tests	Baseline and as clinically indicated (more frequently when used in combination with nivolumab)
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

Monitor Type	Monitor Frequency
INR for patients receiving warfarin	Baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- cabozantinib - For the treatment of advanced renal cell carcinoma (RCC) according to clinical criteria
- cabozantinib - For the treatment of unresectable, advanced hepatocellular carcinoma (HCC) according to clinical criteria

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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.

Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203

CABOSUN trial. J Clin Oncol 2017 Feb 20;35(6):591-7.

Choueiri TK, Escudier B, Powels T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomized, open-label, phase 3 trial. Lancet Oncol 2016;17(7):917-927.

EPAR - Product Information: Cabometyx™ (cabozantinib tablets). Ipsen Pharma, September 2018.

Prescribing Information: Cabometyx ® Exelixis, Inc. Alameda, CA 94502. September 2021.

Product Monograph: Cabometyx ™ (cabozantinib tablets). Ipsen Biopharmaceuticals Canada Inc., October 2021.

Product Monograph Update: Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs). Health Canada InfoWatch, June 2020.

March 2022 Updated all sections of drug monograph

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L - Disclaimer

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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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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