DRUG NAME: Cabozantinib

SYNONYM(S): cabozantinib (*S*)-malate, [1,2] XL 184 [3]

COMMON TRADE NAME(S): CABOMETYX®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Cabozantinib is an orally administered, small molecule tyrosine kinase inhibitor that inhibits multiple receptor kinases, including hepatocyte growth factor receptor protein (MET), vascular endothelial growth factor (VEGF), and fms-like tyrosine kinase-3 (FLT3). Cabozantinib induces cancer cell apoptosis and suppresses tumour growth, angiogenesis, and metastasis. [1,2,4]

PHARMACOKINETICS:

Oral Absorption	may undergo enterohepatic recirculation; steady state by approximately day 15	
Distribution	highly protein bound	
	cross blood brain barrier?	yes [5]
	volume of distribution	319 L
	plasma protein binding	>99%
Metabolism	CYP 3A4 (major), CYP 2C9 (minor) [1,4]	
	active metabolite(s)	weakly active: XL 184-N-oxide, XL 184 amide cleavage product
	inactive metabolite(s)	XL 184 monohydroxy sulfate, 6-desmethyl amide cleavage product sulfate
Excretion	mainly fecal elimination	
	urine	27%
	feces	54%
	terminal half life	99 h
	clearance	2 L/h

Adapted from standard reference [1] unless specified otherwise.

USES:

Primary uses:

*Renal cell cancer

*Liver cancer

*Thyroid cancer

Other uses:

*Health Canada approved indication

Developed: 1 June 2019
Revised: 1 April 2025

SPECIAL PRECAUTIONS:

Caution:

- ***arterial aneurysm*** and ***artery dissection***, including rupture, have been reported in patients with and without hypertension; ensure hypertension is well controlled prior to starting treatment [6]
- ***arterial*** and ***venous thromboembolic events***, including pulmonary embolus, are associated with cabozantinib; use caution in patients at risk for, or who have a history of these events [1,2]
- ***bradycardia*** and ***PR interval prolongation*** have been reported; use caution in patients with baseline heart rate <60 beats per minute or a history of conduction abnormalities, arrhythmia, ischemic heart disease, or congestive heart failure [1]
- ***gastrointestinal perforation*** and ***fistulas*** have been reported; use caution in patients with a history of inflammatory bowel disease, prior GI surgery and/or metastases to the GI tract [1]
- severe ***hemorrhagic events*** have been reported; patients with a history of hemorrhage or other risk factors for bleeding should be evaluated prior to initiating therapy [1]
- ***hypertension*** and ***hypertensive crisis*** have been observed with cabozantinib; hypertension should be well controlled prior to starting treatment [1]
- ***impaired wound healing*** has been associated with cabozantinib; hold cabozantinib for at least 28 days prior to surgery, including dental surgery, and discontinue permanently if wound complications require medical intervention [1]
- ***osteonecrosis of the jaw*** has been reported; consider dental referral prior to treatment initiation and hold cabozantinib for at least 28 days prior to invasive dental procedures [2,4]
- ***QT interval prolongation*** has been reported; monitor ECG and electrolytes in patients with known history of QT prolongation, risk factors for torsades de pointes, or taking concurrent medications known to prolong the QT interval [1]
- cabozantinib dose modification may be required for ***drug interactions*** involving the CYP 3A4 metabolic pathway [7]

Carcinogenicity: In animal studies, an increased incidence of malignant pheochromocytoma was observed. [1] The long-term carcinogenic potential of cabozantinib is unknown based on non-clinical findings. [7]

Mutagenicity: Not mutagenic in Ames test. Cabozantinib was not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. [1]

Fertility: In animal studies, cabozantinib was associated with reduced fertility in male and female test subjects at exposures significantly lower than those expected in humans at therapeutic doses. [7] Hypospermia and decreased reproductive organ weights were reported in males. Decreased live embryos, increased pre-implantation losses, absence of corpora lutea, and ovarian necrosis were reported in females. [1,8] Male and female patients of reproductive should consider fertility preservation before treatment. [7]

Pregnancy: In animal studies, embryo-fetal toxicity (e.g., post-implantation loss, cleft palate, reduced spleen size, and small or missing lung lobe) was reported and occurred at exposures significantly below human therapeutic levels. Female patients of childbearing potential and female partners of male patients should use contraception during treatment and for at least four months after the last dose of cabozantinib to prevent pregnancy. The efficacy of hormonal contraceptives may be reduced due to a possible interaction with cabozantinib; therefore, females using hormonal contraceptives are advised to discuss contraceptive options with their physician. [1]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women may begin breastfeeding four months after the last dose of cabozantinib. [1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be

Developed: 1 June 2019
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clinically important. [9,10] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group. [3,11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (17-18%, severe 1-6%) [4,12]
	hemorrhage (severe 2-3%) [1,4]; has been fatal
	leukopenia (35%, severe <1%) [1]
	lymphopenia (25-53%, severe 7-16%) [1,4]
	neutropenia (31-35%, severe 2-3%) [1,4]
	thrombocytopenia (11-35%, severe ≤3%) [1,4,11]
cardiac	bradycardia [1]
endocrine	***hypothyroidism*** (23%) [12]; thyroid replacement may be necessary
gastrointestinal	*emetogenic potential: moderate* [13]
	abdominal pain (19-27%, severe 3-4%) [3,4,12]
	constipation (25-28%, severe <1%) [3,4,12]
	diarrhea (54-75%, severe 10-22%) [3,11,12]
	dyspepsia (10-12%, severe <1%) [11,12]
	dysphagia (13%)
	flatulence (10%) [12]
	gastrointestinal fistula (1%) [1,2]; see paragraph following **Side Effects** table
	gastrointestinal perforation (1-3%) [1,4]; see paragraph following **Side Effects** table
	hemorrhoids (9%)
	mouth pain (36%)
	mucositis (19%)
	nausea (31-53%, severe 2-5%) [3,11,12]
	pancreatitis (≤2%) [1,4]
	stomatitis (13-51%, severe 2%) [11,12]
	vomiting (24-34%, severe ≤2%) [4,11,12]
general disorders and administration site conditions	asthenia (19-25%, severe 5-7%) [3,4,12]
	edema, peripheral (12%) [12]
	fatigue (41-59%, severe 10-11%) [3,4,12]
	fever (10%, severe 1%) [12]
	fistula, non-gastrointestinal (4%, severe ≤4%) [4]; see paragraph following **Side Effects** table
	mucosal inflammation (14-25%, severe 2-3%) [3,11]
	pain (severe 5%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
hepatobiliary	hepatic encephalopathy (severe <1%) [1]
	hepatic failure (severe <1%) [1]; has been fatal
	hepatitis, cholestatic (≤2%) [1,4]
infections and infestations	pulmonary infection (severe 2-4%) [4,12]
injury, poisoning, and procedural complications	***wound complication*** (≤2%) [1,4]
investigations	alkaline phosphatase increase (35-52%, severe 2%) [1,4]
	ALT increase (17-86%, severe 2-5%) [3,4,12]
	AST increase (19-86%, severe 2-12%) [4,11,12]
	bilirubin increase (25%)
	creatinine increase (5%, severe <1%) [12]
	gamma-glutamyltransferase increase (27%, severe 5%) [1]
	PR interval prolonged [1]
	QTc interval prolonged [1]
	weight loss (17-58%, severe 1-10%) [3,11]
metabolism and nutrition	***anorexia*** (47-49%, severe 3-7%) [3,12]
	dehydration (7%)
	hyperglycemia (5%, severe 1%) [12]
	hyperkalemia (severe 1%)
	hypertriglyceridemia (6%, severe 1%) [12]
	hypoalbuminemia (12-36%, severe ≤2%) [1,11]
	hypocalcemia (24-52%, severe 11%) [3,4]
	hypokalemia (18%)
	hypomagnesemia (16-31%, severe 5%) [4,12]
	hyponatremia (10-30%, severe 8%) [1,4]
	hypophosphatemia (28-48%, severe 8%) [1,4]
musculoskeletal and connective tissue	arthralgia (11-14%, severe <1%) [4,12]
	back pain (18-22%, severe 2-4%) [3,4,12]
	bone pain (severe 3%)
	extremity pain (15-21%, severe 2%) [3,12]
	muscle spasm (12-14%) [4,12]
	musculoskeletal chest pain (9%)
	osteonecrosis of the jaw (≤2%) [1,4]; see paragraph following **Side Effects** table
nervous system	dizziness (11-14%, severe <1%) [4,12]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dysgeusia (12-35%, severe <1%) [3,11]
	headache (11-18%, severe <1%) [4,12]
	paresthesia (7%)
	peripheral neuropathy (5%)
	peripheral sensory neuropathy (7%)
	reversible posterior leukoencephalopathy syndrome (<1%) [1,4]; see paragraph following **Side Effects** table
	seizure (≤2%, severe 1%) [1,4,12]
	syncope (severe 5%)
psychiatric	anxiety (9%)
	confusion (severe 1%)
	depression (severe 4%)
	insomnia (10%) [12]
renal and urinary	acute renal failure (severe 4%)
	proteinuria (2-14%, severe 2%) [4,12]
respiratory, thoracic and mediastinal	cough (21%, severe <1%) [12]
	dysphonia (19-22%, severe ≤1%) [3,11,12]
	dyspnea (20%, severe 3%) [12]
	epistaxis (4%) [12]
	pleural effusion (severe 2%) [12]
skin and subcutaneous tissue	alopecia (16%)
	dermal ulcer (severe 3%)
	dry skin (11-20%) [1,3]
	erythema (11%)
	hair colour change (34%, severe <1%) [3]
	hyperkeratosis (7%)
	palmar-plantar erythrodysesthesia (PPE) (42-53%, severe 8-17%) [3,4,11,12]; see paragraph following **Side Effects** table
	pruritus (8%) [12]
	rash (12-23%, severe <1%) [4,11]
vascular	arterial aneurysm, arterial dissection (<1%) [6]; including rupture
	arterial thromboembolism (severe ≤2%) [1,4]
	hypertension (29-61%, severe 9-16%) [3,4,11]; see paragraph following **Side Effects** table
	hypertensive crisis (severe <1%) [1]; see paragraph following **Side Effects** table
	hypotension (7%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pulmonary embolism (severe 2-5%) [4,12]
	vascular disease (severe 1%)
	venous thromboembolism (6-9%) [1,4]

Adapted from standard reference [4] unless specified otherwise.

Gastrointestinal perforation and ***fistulas*** (GI and non-GI) are rare but may be fatal. Symptoms include severe abdominal pain, nausea, vomiting, and fever or chills. Persistent or recurring diarrhea may increase the risk of developing an anal fistula. Permanently discontinue cabozantinib following a GI perforation or a fistula that cannot be managed. [14]

Hypertension is reported in up to 61% of patients. Hypertensive crisis is rare. Increased blood pressure typically occurs early in treatment; therefore, close monitoring of blood pressure is recommended for at least the first eight weeks of treatment. Hypertension may be managed with standard anti-hypertensive therapy plus cabozantinib dose reduction or interruption. Discontinue cabozantinib for hypertensive crisis or severe hypertension which persists despite anti-hypertensive therapy. [1]

Osteonecrosis of the jaw (ONJ) has been rarely associated with cabozantinib, and may manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth/periodontal infection, gingival ulceration/erosion, or delayed healing of the mouth or jaw. Baseline dental assessments and good oral hygiene are recommended for the prevention of ONJ. Hold cabozantinib for at least 28 days prior to invasive dental procedures. Permanently discontinue cabozantinib if ONJ develops during treatment. [1,2,4] For general information regarding management of ONJ, refer to *Bisphosphonates and Osteonecrosis of the Jaw* in ***Oral & Dental Care: Osteonecrosis of the Jaw.***

Palmar-Plantar Erythrodysesthesia (PPE), also known as hand-foot syndrome, is reported in up to 53% of patients receiving cabozantinib. Up to 17% of those cases are rated as grade 3 or 4 in severity. PPE usually appears during the first eight weeks of treatment. Hold cabozantinib in patients who develop intolerable grade 2 or greater PPE. Resume cabozantinib at a reduced dose upon improvement of symptoms to grade 1 or less. [1,2]

Reversible posterior leukoencephalopathy syndrome (RPLS), a rare neurologic disorder, has been reported with cabozantinib. Symptoms may include seizures, headache, altered mental status, and visual disturbances, with or without associated hypertension. Brain imaging is necessary to confirm diagnosis. Management is usually supportive, with control of hypertension, electrolyte replacement, seizure management, and permanent discontinuation of cabozantinib. Although usually reversible, permanent disability and fatalities have been reported in RPLS cases involving other drugs. [1,2,4,15]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
esomeprazole [1]	no effect on AUC of cabozantinib		
grapefruit juice [1]	may increase plasma level of cabozantinib	may inhibit CYP 3A4 metabolism of cabozantinib in the intestinal wall	avoid grapefruit and grapefruit juice for the duration of treatment with cabozantinib

Developed: 1 June 2019
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AGENT	EFFECT	MECHANISM	MANAGEMENT
ketoconazole [1]	29% decrease in clearance and 38% increase in AUC of cabozantinib	strong inhibition of CYP 3A4 by ketoconazole	avoid concurrent therapy if possible; if unavoidable, reduce daily cabozantinib dose by 20 mg [7] and monitor for cabozantinib toxicity
rifampin [1]	4 fold increase in clearance and 77% decrease in AUC of cabozantinib	strong induction of CYP 3A4 by rifampin	avoid concurrent therapy if possible; if unavoidable, increase daily cabozantinib dose by 20 mg as tolerated, to a maximum of 80 mg daily [7]

Cabozantinib is a substrate of CYP 3A4. If coadministered with a strong CYP 3A4 inhibitor, reduce the daily dose of cabozantinib by 20 mg. Cabozantinib may be resumed at the previous dose 2-3 days after discontinuation of the strong CYP 3A4 inhibitor. If coadministered with a strong CYP 3A4 inducer, increase the daily dose of cabozantinib by 20 mg as tolerated (to a maximum daily dose of 80 mg daily). Cabozantinib may be resumed at the previous dose 2-3 days after discontinuation of the strong CYP 3A4 inducer. [7]

In vitro cabozantinib is a substrate of MRP2; clinical significance is unknown. [1,4]

In vitro, cabozantinib is a moderate inhibitor of P-glycoprotein; clinical significance is unknown. [1]

Cabozantinib is associated with PR and QTc interval prolongation and bradycardia. Avoid concurrent therapy with other drugs associated with PR/QTc prolongation, torsades de pointes, bradycardia, and/or drugs that disrupt electrolyte levels. If concurrent therapy is unavoidable, monitor for PR/QTc prolongation and/or cardiac arrhythmias. [1]

SUPPLY AND STORAGE:

Oral: Ipsen Biopharmaceuticals Canada, Inc. supplies cabozantinib (as cabozantinib (*S*)-malate) as 20 mg, 40 mg, and 60 mg film-coated tablets. Tablets contain lactose. Store at room temperature. [1]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral:

60 mg (range 20-60 mg)* ***PO once daily**** [16-18]

* dose adjustment may be required for some drug interactions[7]
** lowest recommended dose reduction may require administration every other day (e.g., 20 mg PO every other day)[7]

Administer on an empty stomach (1 h before meals or 2 h after). [7]

Concurrent radiation: no information found

Developed: 1 June 2019
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BC Cancer usual dose noted in ***bold, italics***

Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required [1,2,4] CrCl <30 mL/min: no information found calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	mild or moderate impairment (Child-Pugh A or B): 40 mg PO once daily [1,4] severe impairment (Child-Pugh C): avoid [1,4]
Dosage in dialysis:	no information found

Children: safety and efficacy have not been established

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Developed: 1 June 2019
Revised: 1 April 2025