Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

selpercatinib

COMMON TRADE NAME(S): Retevmo™

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B - Mechanism of Action and Pharmacokinetics

Selpercatinib is a selective inhibitor of RET (rearranged during transfection) kinase. *In vitro*, selpercatinib inhibited wild type RET, multiple mutated forms of RET, VEGFR3 (FLT4), VEGFR1 (FLT1), and FGFR1, 2 and 3 at higher concentrations.

Point mutations in RET or chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins, that can act as oncogenic drivers by promoting cell proliferation and survival in tumor cell lines.

Absorption	Bioavailability	73% (mean)
	Effects with food	Food is unlikely to have clinically important effects. Administration with a high-fat, high calorie meal ↑ AUC by 9%, ↓ C_{max} by 14%, and ↑ T_{max} to 4.0 hours.
	T max	2 h (mean)
	Time to reach steady state	7 days

Distribution	The volume of distribution of selpercatinib increases with increasing body weight.	
	Cross blood brain barrier?	Yes
	PPB	97%
Metabolism	Selpercatinib is metabolized predominantly by CYP3A4.	
	Active metabolites	Unknown
	Inactive metabolites	Unknown
Elimination	The clearance of selpercatinib increases with increasing body weight.	
	Feces	69% (14% unchanged)
	Urine	24% (12% unchanged)
	Half-life	24.5 h (mean)

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C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer (NSCLC)
- Medullary thyroid cancer (MTC)
- Differentiated thyroid carcinoma (DTC)

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following adverse effects were reported in ≥ 10% of patients with advanced solid tumours treated with selpercatinib in a Phase 1/2 multi-cohort study. Severe or life-threatening adverse effects are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (<10%)	E
	Bradycardia (<10%)	E
	Hypertension (43%) (20% severe)	E
	Pericardial effusion (<10%)	E
	QT interval prolonged (21%) (5% severe)	E
	Venous thromboembolism (<10%)	E
Dermatological	Alopecia (10%)	E D
	Rash (38%)	E
Gastrointestinal	Abdominal pain (37%)	E
	Anorexia, weight loss (22%)	E
	Ascites (15%) (2% severe)	E
	Constipation (35%)	E
	Diarrhea (50%) (6% severe)	E
	Dry mouth (44%)	E
	Mucositis (17%)	E
	Nausea, vomiting (35%)	E
	Other (<10%) - chylothorax	L
	Weight gain (12%)	E
General	Edema (52%) (1% severe)	E
	Fatigue (49%) (4% severe)	E
Hematological	Hemorrhage (24%) (3% severe)	E
	Myelosuppression ± infection (17%) (6% severe)	E
Hepatobiliary	↓ albumin (15%)	E
	↑ Bilirubin (12%)	E
	↑ LFTs (38%) (12% severe)	E
Hypersensitivity	Hypersensitivity (6%)	E

Metabolic / Endocrine	Abnormal electrolyte(s) (17%) (including ↓ Ca, ↓ Na, ↓ Mg, ↓/↑ K, ↑ PO4; 9% severe)	E
	Hyperthyroidism (<10%)	E
	Hypothyroidism (16%)	E
	Tumour lysis syndrome (1%)	E
Musculoskeletal	Musculoskeletal pain (23%)	E
Nervous System	Dizziness (21%)	E
	Headache (29%)	E
	Insomnia (16%)	E
Renal	Creatinine increased (30%) (2% severe)	E
Reproductive and breast disorders	Erectile dysfunction (16%)	E
Respiratory	Cough, dyspnea (27%)	E
	Pleural effusion (14%) (3% severe)	E
	Pneumonitis (<10%)	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 selpercatinib include edema, diarrhea, fatigue, dry mouth, hypertension, ↑ LFTs, rash, abdominal pain, constipation, nausea and vomiting.

Severe bleeding (including CNS, respiratory) or **pneumonitis** can occur with selpercatinib, and may be fatal.

New onset or worsening of hypothyroidism may occur with treatment.

The median time to onset for ↑ ALT or AST was ~5 weeks.

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E - Dosing

Refer to protocol by which the patient is being treated.

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

Confirm RET gene fusion or mutation using a validated test before initiation.

Hypertension should be well-controlled prior to initiation of treatment.

Patients must have a QTcF interval of ≤ 470 ms and serum electrolytes within normal range before starting treatment.

Consider appropriate prophylaxis including hydration for patients at risk of tumour lysis syndrome (e.g. rapidly growing tumors, high tumor burden, renal dysfunction, or dehydration).

Hold selpercatinib for ≥ 7 days prior to elective surgery. Do not administer for ≥ 2 weeks following major surgery and until adequate wound healing.

Adults:

Oral: 120 mg BID in patients with body weight (BW) of < 50 kg

Oral: 160 mg BID in patients with body weight (BW) of ≥ 50 kg

Refer to Interactions section for dosing recommendations when co-administered with **CYP3A4 inhibitors.**

Dosage with Toxicity:

Dose Levels	Selpercatinib Dose < 50 kg BW	Selpercatinib Dose ≥ 50 kg BW
0	120 mg twice daily	160 mg twice daily
-1	80 mg twice daily	120 mg twice daily
-2	40 mg twice daily	80 mg twice daily
-3	40 mg **once** daily	40 mg twice daily
-4	Discontinue	Discontinue

Toxicity	Severity	Action
QT Prolongation	Grade 3	Hold until resolved to Grade 1 or baseline. Resume at 1 dose level ↓. If recurs despite **2** dose reductions, discontinue.
	Grade 4 or signs and symptoms of serious arrhythmia	Discontinue.
↑ AST or ALT	Grade 3 or 4	Hold until resolved to Grade 1 or baseline; monitor AST or ALT weekly. Resume at **2** dose levels ↓; continue AST or ALT weekly monitoring. Increase by 1 dose level after ≥ 2 weeks without recurrence, and then increase to dose taken prior to the onset of toxicity after ≥ 4 weeks without recurrence. Continue AST or ALT weekly monitoring for 4 weeks thereafter. If recurs despite dose reductions, discontinue.
Hypersensitivity	Any	Hold until resolved; begin steroid treatment. Resume at **3** dose levels ↓ while continuing steroid treatment. Increase selpercatinib by 1 dose level weekly if no recurrence. Taper steroid dose after selpercatinib has been tolerated for ≥ 7 days at the dose taken prior to the onset of toxicity. If recurs despite dose reductions, discontinue.
Hypertension	Grade 3	Hold until controlled with medical management. Resume at 1 dose level ↓.
	Grade 4 or significant hypertension that cannot be controlled with antihypertensive therapy	Discontinue.

Hemorrhagic Events	Grade 3 or 4	Hold until resolved to ≤ Grade 1 or baseline. Discontinue for severe or life-threatening events.
Interstitial Lung Disease / Pneumonitis	Grade 2 that does not resolve to baseline or grade 1 within 7 days (despite maximal supportive measures)	Hold until resolved to Grade 1 or baseline. Resume at 1 dose level ↓.
	Grade 3 or 4	Discontinue.
Other Adverse Reactions	Grade 3 or 4	Hold until resolved to ≤ Grade 1 or baseline. Resume at a reduced dose.

Dosage with Hepatic Impairment:

Limited safety data are available in patients with severe hepatic impairment; monitor ALT and AST more frequently as clinically indicated.

Hepatic Impairment	Selpercatinib Dose (regardless of BW)
Child-Pugh class A or B	No dose adjustment
Child-Pugh class C	80 mg twice daily

Dosage with Renal Impairment:

No dosage adjustment is necessary in patients with mild, moderate or severe renal impairment. Selpercatinib is not recommended in patients with end-stage renal disease.

Dosage in the elderly:

No overall differences in safety or efficacy observed between patients ≥ 65 years of age and younger patients.

Dosage based on gender:

Sex had no clinically meaningful effect on the pharmacokinetics of selpercatinib.

Dosage based on ethnicity:

Ethnic origin had no clinically meaningful effect on the pharmacokinetics of selpercatinib.

Children:

Selpercatinib is indicated by Health Canada in patients 12-17 years of age with unresectable advanced or metastatic RET-mutant MTC.

There are no pharmacokinetics data of selpercatinib in patients younger than 15 years of age. The safety and efficacy of selpercatinib have not been established in patients < 12 years of age.

The safety of long-term use of selpercatinib has not been evaluated in adolescent patients. Selpercatinib is associated with a potential risk for delayed growth or bone-related adverse effects; additional monitoring is recommended.

Refer to product monograph for more information.

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F - Administration Guidelines

- Administer selpercatinib with or without food. Refer to Interaction section when given concomitantly with PPIs, H2 receptor antagonists, or antacids.
- Capsules should be swallowed whole with a glass of water and not opened, crushed, or chewed.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during selpercatinib treatment.
- If a dose is missed, the dose may be taken if there are ≥ 6 hours until the next dose. If there are < 6 hours until the next dose, the dose should be skipped and the next dose should be taken at the scheduled time. Patients should not take 2 doses at the same time to make up for a missed dose.
- If the patient vomits after taking a dose, an additional dose should not be taken. The next dose should be continued as scheduled.
- Store at room temperature (15° to 30°C).

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Avoid use of selpercatinib in patients with conditions that may increase the risk of experiencing torsade de pointes.
- Patients should exercise caution when driving or operating a vehicle or potentially dangerous machinery as dizziness has been reported.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Genotoxicity: Yes
- Teratogenicity: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Pregnancy:
  Selpercatinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **2 weeks** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **2 weeks** after the last dose.
- Fertility effects: Probable
  - Documented in animal studies.
  - May impair fertility in both genders

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H - Interactions

Selpercatinib is a substrate of CYP3A4 and is predominantly metabolized by CYP3A4.

Selpercatinib is a substrate and inhibitor of P-gp and BCRP.

In addition, selpercatinib inhibits the renal transporter MATE1 and may increase **serum creatinine** without affecting glomerular function. Consider alternative markers of renal function (e.g. cystatin C, BUN, or calculated GFR) with persistent elevations in serum creatinine.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, voriconazole, ketoconazole, ritonavir, posaconazole)	↑ selpercatinib exposure and/or toxicity, including QTc prolongation (↑ AUC by 133% with itraconazole)	↓ metabolism of selpercatinib	Avoid concomitant use. If unavoidable, ↓ selpercatinib dose and perform ECG more frequently. Refer to table below.
Moderate CYP3A4 inhibitors (e.g. diltiazem, fluconazole, verapamil, ciprofloxacin)	↑ selpercatinib exposure and/or toxicity, including QTc prolongation	↓ metabolism of selpercatinib	Avoid concomitant use. If unavoidable, ↓ selpercatinib dose and perform ECG more frequently. Refer to table below.
Strong CYP3A4 inducers (e.g. rifampin, phenytoin, phenobarbital, carbamazepine, dexamethasone, rifabutin, St. John's Wort)	↓ selpercatinib effect	↑ metabolism of selpercatinib	Avoid concomitant use.
Moderate CYP3A4 inducers (e.g. bosentan, efavirenz)	↓ selpercatinib effect	↑ metabolism of selpercatinib	Avoid concomitant use.
Sensitive CYP3A4 substrates (e.g. midazolam, buspirone, lovastatin, naloxegol, simvastatin, tipranavir, triazolam, vardenafil)	↑ substrate exposure (↑ AUC by 54% with midazolam)	Selpercatinib is a weak CY3A4 inhibitor.	Avoid concomitant use. If unavoidable, ↓ substrate dose as per product monograph.

Sensitive CYP2C8 substrates (e.g. repaglinide)	↑ substrate exposure (↑ AUC by 188% with repaglinide)	Selpercatinib is a moderate CYP2C8 inhibitor.	Avoid concomitant use. If unavoidable, ↓ substrate dose as per product monograph.
PPIs (e.g. omeprazole)	↓ selpercatinib exposure (↓ AUC by 69% with omeprazole when fasting)	pH dependent solubility; reduced gastric acidity ↓ bioavailability of selpercatinib.	Avoid coadministration. If unavoidable, administer selpercatinib with food.
H2 receptor antagonists (e.g. ranitidine)	↓ selpercatinib bioavailability	pH dependent solubility; reduced gastric acidity ↓ bioavailability of selpercatinib.	Avoid coadministration. If unavoidable, administer selpercatinib 2 hours before or 10 hours after H2 receptor antagonist.
Antacids (e.g. calcium carbonate)	↓ selpercatinib bioavailability	pH dependent solubility; reduced gastric acidity ↓ bioavailability of selpercatinib.	Avoid coadministration. If unavoidable, administer selpercatinib 2 hours before or 2 hours after antacids.
BCRP substrates	↑ risk of substrate toxicity	Selpercatinib is an inhibitor of BCRP	Caution. Avoid concomitant use with substrates with a narrow therapeutic range. If unavoidable, follow recommendations for BCRP substrates as per product monograph.
P-gp substrates with a narrow therapeutic range (e.g. dabigatran)	↑ risk of substrate toxicity	Selpercatinib is an inhibitor of P-gp	Avoid concomitant use. If unavoidable, follow recommendations for P-gp substrates as per product monograph.

Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QTc prolongation	Additive	Avoid concomitant use. If unavoidable, monitor ECG and electrolytes.
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of QTc prolongation	Additive	Avoid concomitant use if possible.
Drugs that reduce heart rate (e.g. beta-blockers, digitalis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists)	↑ risk of QTc prolongation	Bradycardia is a risk for QT prolongation.	Avoid concomitant use.

Dose Modification when Co-administered with CYP3A4 Inhibitors

Planned Selpercatinib Dose (mg twice daily)	Selpercatinib Dose (mg twice daily)	
	with Moderate CYP3A4 inhibitor*	with Strong CYP3A4 inhibitor*
120	80	40
160	120	80

*After the inhibitor has been discontinued for 3 to 5 elimination half-lives of the inhibitor, resume selpercatinib at the dose taken before starting the CYP3A4 inhibitor.

There is no data on the safety of concomitant use of CYP3A inhibitors in patients whose dose was previously reduced due to adverse effects.

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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

Monitor Type	Monitor Frequency
Liver function tests	Baseline, every 2 weeks for 3 months after initiation, then monthly, and as clinically indicated.
ECG	Baseline, 1 week after initiation, then monthly for 6 months, and as clinically indicated
Electrolytes, including K, Mg, Ca	Baseline, 1 week after initiation, then monthly for 6 months, and as clinically indicated
Blood pressure	Baseline, 1 week after initiation, then monthly for 6 months, and as clinically indicated
CBC	Baseline, monthly, and as clinically indicated
Thyroid function tests	Baseline and as clinically indicated
Renal function tests*	Baseline and as clinically indicated
Clinical toxicity assessment for hypersensitivity, pneumonitis, TLS, infection, bleeding, delayed wound healing (if applicable), GI, and cardiovascular effects	At each visit

*Selpercatinib may increase serum creatinine, without affecting glomerular function, by inhibiting renal tubular secretion transporters. Consider alternative markers that are not based on creatinine (e.g. BUN) for determining renal function.

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

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- selpercatinib - For the treatments of advanced or metastatic RET fusion-positive differentiated thyroid carcinoma (DTC); and unresectable advanced or metastatic RET-mutant medullary thyroid cancer (MTC)
- selpercatinib - For the treatment of metastatic RET fusion-positive non-small cell lung cancer (NSCLC)

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K - References

CADTH reimbursement recommendation: selpercatinib (metastatic RET fusion-positive non-small cell lung cancer). May 2022.

Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of Selpercatinib in *RET* Fusion-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Aug 27;383(9):813-824.

Herrstedt J, Clark-Snow R, Ruhlmann CH, et al. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO Open. 2024;9(2):102195.

NCCN Clinical Practice Guidelines in Oncology. Antiemesis. NCCN Guidelines Version 2.2024.

Prescribing information: RETEVMO® (selpercatinib) capsules. Eli Lilly and Company. Sept 2022.

Product monograph: Selpercatinib (Retevmo™). Loxo Oncology, Inc. January 10, 2025.

April 2025 New 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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