# DRUG NAME: Selpercatinib

**SYNONYM(S):** LOXO-292[1]

**COMMON TRADE NAME(S):** RETEVMO®

**CLASSIFICATION:** molecular targeted therapy

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

## MECHANISM OF ACTION:

Selpercatinib is an orally administered selective RET (REarranged during Transfection) tyrosine kinase inhibitor. The RET kinase protein, which is encoded by the RET proto-oncogene, is involved in cell signaling, proliferation, and differentiation. RET gene fusions or mutations can lead to ligand-independent constitutive activation of the RET kinase signaling pathway. Selpercatinib binds to the ATP-binding site and locks the kinase in the inactive state, preventing downstream signaling and cell proliferation. Selpercatinib has demonstrated its activity against wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3. *In vitro* selpercatinib also inhibits fibroblast growth factor receptor (FGFR) 1, 2, and 3.[2-6]

## PHARMACOKINETICS:

| | | |
|---|---|---|
| Oral Absorption | $T_{max}$ = 2 h; time to steady state = 7d | |
| Distribution | highly bound to plasma proteins; fraction of unbound selpercatinib is significantly increased in hepatic insufficiency (Child-Pugh C) | |
| | cross blood brain barrier? | yes[1] |
| | volume of distribution | 191 L |
| | plasma protein binding | 97% |
| Metabolism | primarily metabolized by CYP 3A4 | |
| | active metabolite(s) | no information found |
| | inactive metabolite(s) | no information found |
| Excretion | primarily by fecal elimination | |
| | urine | 24% (12% as unchanged drug) |
| | feces | 69% (14% as unchanged drug) |
| | terminal half life | 24.5-32 h |
| | clearance | 6 L/h |
| Sex | no clinically significant difference | |
| Elderly | no clinically significant difference | |
| Ethnicity | no clinically significant difference | |

Adapted from standard reference[2-4] unless specified otherwise.

## USES:

***Primary uses:***

*Lung cancer, non-small cell

*Thyroid cancer

***Other uses:***

Solid tumours, RET gene fusion-positive[3]

*Health Canada approved indication



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## SPECIAL PRECAUTIONS:

***Caution:***
- patients with severe ***hepatic impairment*** (Child-Pugh C) require a reduced starting dose and more frequent monitoring of AST/ALT[2,3]
- pre-existing ***hypertension*** should be adequately controlled prior to starting treatment[2,3]
- selpercatinib dose reduction may be required for ***drug interactions*** involving the CYP 3A4 metabolic pathway[2,3]
- ***QTc prolongation*** has been reported; correct electrolyte abnormalities prior to treatment and monitor ECG and electrolytes in patients with known risk factors[2,3]
- selpercatinib has been associated with ***impaired wound healing*** and ***bleeding***; withholding selpercatinib may be required in patients undergoing surgical procedures[2,3]
- patients with a high tumour burden, rapidly growing tumour, renal dysfunction, or dehydration may be at increased risk of ***tumour lysis syndrome***[2]

***Special populations: Pediatric patients*** with open growth plates may be at increased risk of delayed growth if treated with selpercatinib. In juvenile animal studies, epiphyseal growth plate hypertrophy, decreased femur length, reduced bone mineral density, and tooth abnormalities (e.g., tooth dysplasia, tooth discolouration, and malocclusion) were observed. Some effects were irreversible. Monitor for growth plate abnormalities in patients with open growth plates.[2]

***Carcinogenicity:*** Carcinogenicity studies have not been conducted.[2,3]

***Mutagenicity:*** Not mutagenic in Ames test. Selpercatinib was clastogenic in the mammalian *in vivo* chromosome test, but was not clastogenic in mammalian *in vitro* chromosome test.[2,3]

***Fertility:*** In animal studies, male test subjects exhibited testicular degeneration, reduced luminal sperm in the epididymis, and dose-dependent testicular germ cell depletion and spermatid retention at exposures less than those seen following human clinical exposure. Altered sperm morphology was observed at exposures approximately twice the expected human clinical exposure. Reproductive performance was also affected when juvenile male test subjects were later mated as adolescents with untreated females. Observed effects included: lower male fertility and copulation indices, increased pre- and post-implantation losses, and fewer viable embryos. In female test subjects, the number of estrous cycles was reduced, and there were fewer viable embryos and increased post-implantation losses at exposure similar to those seen following human clinical exposure. Decreased or absent corpora lutea and the presence of corpora luteal cysts were reported at exposure less than those seen following human clinical exposure.[2,3] Selpercatinib may impair fertility in men and women of reproductive potential.[2]

***Pregnancy:*** In animal studies, selpercatinib was teratogenic and caused embryofetal toxicity. Structural malformations, early resorptions, decreased fetal body weights, increased post-implantation losses, and fewer viable fetuses were observed at exposures similar to, or higher, than those seen following human clinical exposure.[2] Pregnancy tests are recommended prior to starting treatment for female patients of childbearing potential. Contraception is recommended during treatment and at least 2 weeks after the last dose of selpercatinib for female patients of childbearing potential and male patients with female partners of childbearing potential.[2]

***Breastfeeding*** is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 2 weeks after the last dose of selpercatinib.[2]

## 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 clinically important.[7,8]



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia | anemia (9%, severe 4%)[9] |
| | leukopenia (10-52%, severe 1-2%) |
| | lymphopenia (10-44%, severe 4-20%) |
| | neutropenia (19-25%, severe 3%) |
| | ***thrombocytopenia*** (13-37%, severe 3%) |
| cardiac | cardiac arrest (severe 1%); fatalities reported |
| endocrine | hypothyroidism (13%) |
| eye | periorbital edema |
| gastrointestinal | *emetogenic potential:* low[10] |
| | abdominal pain (23-34%, severe 2-3%) |
| | constipation (25-33%, severe 1%) |
| | chylous ascites (1%) |
| | ***diarrhea*** (36-47%, severe 5%) |
| | dry mouth (38-43%) |
| | gastroesophageal reflux disease (11%) |
| | nausea (22-31%, severe 1%) |
| | vomiting (15-22%, severe 2%) |
| general disorders and administration site conditions | ***edema*** (35-49%, severe 1%) |
| | fatigue (35-46%, severe 2-3%) |
| | pyrexia (14%, severe 1%) |
| hepatobiliary | liver injury (2%, severe 2%)[9] |
| immune system | ***hypersensitivity*** (4-6%, severe 2%); see paragraph following **Side Effects** table |
| infections and infestations | pneumonia (severe 4%)[11]; fatalities reported |
| | urinary tract infection (11%, severe 1%) |
| | sepsis (severe 1%); fatalities reported |
| investigations | albumin decrease (42-56%, severe 1-2%) |
| | alkaline phosphatase increase (11-40%, severe 1-3%) |
| | ***ALT increase*** (29-56%, severe 9-12%) |
| | ***AST increase*** (30-59%, severe 8-11%) |
| | bilirubin increase (23-30%, severe 2%) |
| | calcium decrease (41-59%, severe 4-6%) |
| | cholesterol increase (31-35%, severe 1-2%) |
| | creatinine increase (29-47%, severe 1%) |
| | glucose decrease (22-34%, severe 1%) |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| | glucose increase (44-53%, severe 2-3%) |
| | hemoglobin decrease (19-28%, severe 1-4%) |
| | magnesium decrease (24-33%, severe 1%) |
| | potassium increase (24-34%, severe 1-3%) |
| | potassium decrease (11%, severe 2%)[9] |
| | ***QTc prolongation*** (17-21%, severe 5%) |
| | sodium decrease (27-42%, severe 7-11%) |
| | weight gain (13%)[9] |
| metabolism and nutrition | appetite decrease (11%, severe <1%) |
| | ***tumour lysis syndrome*** (1%) |
| musculoskeletal and connective tissue | arthralgia (13-21%, severe <1%) |
| | back pain (12%, severe 1%) |
| | myalgia (<10%) |
| nervous system | dizziness (12%) |
| | ***headache*** (23-28%, severe 1%) |
| psychiatric | insomnia (18%)[9] |
| renal and urinary | acute kidney injury (2%, severe 2%)[9] |
| reproductive system and breast disorders | erectile dysfunction (1-10%)[2,12] |
| respiratory, thoracic and mediastinal | cough (18-24%) |
| | ***dyspnea*** (16-22%, severe 3%); fatalities reported |
| | ***interstitial lung disease*** (ILD)/***pneumonitis*** (2%, severe <1%); fatalities reported[3] |
| | ***pleural effusion*** (2%)[4]; chylothorax reported[2] |
| | ***respiratory failure*** (severe 1%); fatalities reported |
| skin and subcutaneous tissue | dry skin (12%) |
| | ***rash*** (27-33%, severe 1%) |
| | pruritus (11%)[9] |
| vascular | ***hemorrhage*** (15-22%, severe 2-3%); see paragraph following **Side Effects** table |
| | ***hypertension*** (35-41%, severe 13-20%) |

Adapted from standard reference[2,3,11] unless specified otherwise.

Fatal ***hemorrhagic events*** have been reported with selpercatinib, including cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Other reported hemorrhagic events include: epistaxis, hematemesis, hematuria, post-procedural hemorrhage, and hemorrhage at various organ sites. Withhold selpercatinib for grade 3 or 4 events and do not restart until event has recovered to grade 1 or less severity. Permanently discontinue selpercatinib for life-threatening events.[2,3]



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***Hypersensitivity*** has been reported in 4-6% of patients. Hypersensitivity reactions due to selpercatinib include a constellation of findings characterized by a maculopapular rash, often preceded by fever, accompanied by arthralgia or myalgia. Concurrent signs and symptoms may include hypotension, tachycardia, and lab abnormalities (e.g., decreased platelets, increased AST/ALT, or increased creatinine).[2,13] Median time to first onset is 2 weeks (range from 1 to 5 weeks).[13] Exact mechanism is not established but may be immune-related. Higher incidence of hypersensitivity has been reported in patients previously treated with immune checkpoint inhibitors.[13] If a hypersensitivity reaction occurs, withhold selpercatinib and begin steroid treatment as indicated. Selpercatinib may be resumed at a reduced dose once the event has resolved. Dose reescalation may be considered if patient tolerates treatment without recurrence of hypersensitivity. Steroid treatment should continue until target dose of selpercatinib is reached and then steroid may be tapered as clinically indicated. Permanently discontinue selpercatinib if hypersensitivity recurs despite dose reductions.[2,3]

***Impaired wound healing*** has been associated with medications that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Temporary interruption of selpercatinib is recommended in patients undergoing minor and major surgical procedures. Consider withholding selpercatinib for a minimum of one week prior to surgery and two weeks following surgery. Selpercatinib may be resumed once adequate wound healing has occurred.[2]

***Increased serum creatinine*** may occur secondary to inhibition of renal transporter MATE1 (multidrug and toxin extrusion protein 1) by selpercatinib. Because creatinine is a substrate of MATE1, selpercatinib can decrease its renal tubular secretion. Glomerular function is not affected. Creatinine level may remain elevated throughout selpercatinib treatment, possibly leading to an incorrect diagnosis of drug related kidney injury.[14] Consider alternative markers to evaluate renal function during treatment, such as calculated GFR (if not based on creatinine), BUN, or cystatin C.[2]

## INTERACTIONS:

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| antacids[2] (e.g., calcium carbonate) | locally acting antacids may decrease absorption of selpercatinib | pH-dependent solubility of selpercatinib (reduced solubility with increasing pH) | avoid concurrent use; if concurrent use cannot be avoided, administer antacids 2 h before or 2 h after selpercatinib |
| dabigatran[2,4] | 38% increase in dabigatran AUC and 43% increase in $C_{max}$ | inhibition of P-gp by selpercatinib | avoid concurrent use in patients with reduced renal function[15]; monitor for toxicity of dabigatran |
| grapefruit juice[2,15,16] | may increase plasma level of selpercatinib | may inhibit CYP 3A4 metabolism of selpercatinib in the intestinal wall | avoid grapefruit juice for the duration of treatment with selpercatinib |
| itraconazole[2] | 133% increase in selpercatinib AUC and 30% increase in $C_{max}$ | strong inhibition of CYP 3A4 by itraconazole | avoid concurrent use; if concurrent use cannot be avoided, see table below for suggested selpercatinib dose reduction and monitor for selpercatinib toxicity and QTc prolongation |
| metformin[2] | no clinically significant changes in blood glucose (effect on metformin $C_{max}$ and AUC is not reported) | inhibition of MATE1 by selpercatinib | not considered clinically significant; monitor blood glucose as clinically indicated |
| midazolam[2,4] | 54% increase in midazolam AUC and 39% increase in $C_{max}$ | inhibition of CYP 3A4 by selpercatinib | monitor for toxicity of midazolam and adjust midazolam dose as required |



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| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| omeprazole[2], proton pump inhibitors | fasted state: 69% decrease in selpercatinib AUC and 88% decrease in $C_{max}$<br>non-fasted state: insignificant change in selpercatinib AUC and $C_{max}$ | pH-dependent solubility of selpercatinib (reduced solubility with increasing pH) | avoid concurrent use; if concurrent use cannot be avoided, administer selpercatinib with food |
| ranitidine[2], $H_2$-blockers | 7% decrease in selpercatinib AUC and 18% decrease in $C_{max}$ (when ranitidine was given 10 h before or 2 h after selpercatinib in a fasted state) | pH-dependent solubility of selpercatinib (reduced solubility with increasing pH) | avoid concurrent use; if concurrent use cannot be avoided, administer ranitidine 10 h before or 2 h after selpercatinib |
| repaglinide[2,4] | 188% increase in repaglinide AUC and 91% increase in $C_{max}$ | inhibition of CYP 2C8 by selpercatinib | avoid concurrent use; if concurrent use cannot be avoided, monitor for hypoglycemia and adjust repaglinide dose as required |
| rifampin[2] | 87% decrease in selpercatinib AUC and 70% decrease in $C_{max}$ | strong induction of CYP 3A4 by rifampin | avoid concurrent use |

Selpercatinib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentration of selpercatinib. Avoid concurrent use with ***moderate*** or ***strong*** CYP 3A4 inhibitors. If coadministration with a moderate or strong CYP 3A4 inhibitor cannot be avoided, reduce selpercatinib dose (see table below). Monitor for selpercatinib toxicity including QTc prolongation.[2] If the CYP 3A4 inhibitor has been discontinued, selpercatinib may be resumed at the prior dose after 3 to 5 half-lives of the inhibitor.[2]

| Planned Selpercatinib Dose | Suggested Selpercatinib Dose Reduction[2] | |
|---|---|---|
| | Coadministered with ***MODERATE* CYP 3A4 Inhibitor** | Coadministered with ***STRONG* CYP 3A4 Inhibitor** |
| 160 mg twice daily | 120 mg twice daily | 80 mg twice daily |
| 120 mg twice daily | 80 mg twice daily | 40 mg twice daily |
| 80 mg twice daily | no information found | |
| 40 mg twice daily | no information found | |
| 40 mg once daily | no information found | |

***CYP 3A4 inducers*** may decrease the plasma concentration of selpercatinib. Avoid concurrent use with ***moderate*** or ***strong*** CYP 3A4 inducers if possible.[2,3]

Selpercatinib ***inhibits CYP 2C8*** and ***P-gp.*** Concurrent use of selpercatinib with a substrate of CYP 2C8 or P-glycoprotein may increase the plasma concentration of the substrate; monitor for toxicity of the substrate.[2]

*In vitro*, selpercatinib is a substrate and an inhibitor of Breast Cancer Resistance Protein (BCRP); clinical significance is unknown.[2]

## SUPPLY AND STORAGE:

***Oral:*** Eli Lilly Canada Inc. supplies selpercatinib as 40 mg and 80 mg capsules. Store at room temperature.[2]



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## 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*[2,17-19]*:* | ***<50 kg: 120 mg PO twice daily**** (range 40 mg once daily-120 mg twice daily)<br>***≥50 kg: 160 mg PO twice daily**** (range 40 mg-160 mg twice daily)<br><br>Administer with food or on an empty stomach.[2]<br>Do not take with grapefruit or grapefruit juice.[2]<br><br>*dose adjustment may be required for some drug interactions[2] |
| *Concurrent radiation:* | no information found |
| *Dosage in myelosuppression:* | modify according to protocol by which patient is being treated |
| *Dosage in renal failure*[2,3]*:* | eGFR ≥15 mL/min/1.73 $m^2$: no adjustment required<br>eGFR <15 mL/min/1.73 $m^2$: no information found |
| *Dosage in hepatic failure*[2,3]*:* | mild to moderate impairment (Child-Pugh A,B): no adjustment required<br>severe impairment (Child-Pugh C): reduce dose to 80 mg twice daily, regardless of body weight |
| *Dosage in dialysis:* | no information found |

***Children*:**

| | |
|---|---|
| *Oral:*[2,3] | children under 12 years of age: safety and efficacy have not been established<br><br>adolescents 12 years and older:<br><50 kg: 120 mg PO twice daily* (range 40 mg once daily-120 mg twice daily)<br>≥50 kg: 160 mg PO twice daily* (range 40 mg-160 mg twice daily)<br><br>Administer with food or on an empty stomach.<br>Do not take with grapefruit or grapefruit juice.<br><br>*dose adjustment may be required for some drug interactions |



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