# DRUG NAME: Ripretinib

**SYNONYM(S):** DCC-2618[1]

**COMMON TRADE NAME(S):** QINLOCK®

**CLASSIFICATION:** molecular targeted therapy

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

## MECHANISM OF ACTION:

Ripretinib is an orally administered potent inhibitor of receptor tyrosine kinases, including KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet-derived growth factor receptor A (PDGFRA). As a type II tyrosine switch-control inhibitor, ripretinib inhibits kinase signaling through a dual mechanism of action. Ripretinib specifically and durably binds to both the switch pocket and the activation loop to lock the kinase in the inactive state, preventing downstream signaling and cell proliferation. This dual mechanism of action broadly inhibits KIT and PDGFRA, including wild-type mutations plus primary and secondary mutations associated with resistance to other tyrosine kinase inhibitors. *In vitro*, ripretinib also inhibits PDGRFB, TIE2, VEGFR2, and BRAF.[2-5]

## PHARMACOKINETICS:

| | | |
|---|---|---|
| Oral Absorption | $T_{max}$ = 4 h (parent compound); 15.6 h (DP-5439 metabolite); time to steady state = 14 d | |
| Distribution | highly bound to plasma proteins | |
| | cross blood brain barrier? | no information found |
| | volume of distribution | 307 L (parent compound); 507 L (DP-5439) |
| | plasma protein binding | ≥99% |
| Metabolism | primarily metabolized by CYP 3A4 | |
| | active metabolite(s) | DP-5439 |
| | inactive metabolite(s) | no information found |
| Excretion | primarily fecal elimination | |
| | urine | 0.02% (parent compound); 0.1% (DP-5439) |
| | feces | 34% (parent compound); 6% (DP-5439) |
| | terminal half life | 14.8 h (parent compound); 17.8 h (DP-5439) |
| | clearance | 15.3 L/h (parent compound); 17.5 L/h (DP-5439) |
| Sex | no clinically significant difference | |
| Elderly | no clinically significant difference | |
| Ethnicity | no clinically significant difference | |

Adapted from standard reference[1,4,5] unless specified otherwise.

## USES:

***Primary uses:***

*Gastrointestinal stromal tumour (GIST)

***Other uses:***

*Health Canada approved indication


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## SPECIAL PRECAUTIONS:

***Caution:***
- assess ***cardiac*** function prior to starting treatment and monitor as indicated throughout treatment[4,5]
- pre-existing ***hypertension*** should be adequately controlled prior to starting treatment[4,5]
- ripretinib dose adjustment may be required for ***drug interactions*** involving the CYP 3A4 metabolic pathway[4,5]
- ***new primary cutaneous malignancies*** including ***squamous cell carcinoma*** and ***melanoma*** have been reported; begin screening for suspicious lesions prior to initiating ripretinib and monitor throughout treatment[4,5]
- ripretinib is potentially ***phototoxic***; exposure to strong sunlight, sunlamps, and other sources of ultraviolet radiation should be avoided or minimized during treatment[5]
- ***wound healing*** may be impaired with ripretinib; consider temporary treatment interruption in patients undergoing surgical procedures[4,5]
- patients who have experienced ***hypersensitivity*** with another tyrosine kinase inhibitor may be at increased risk of hypersensitivity with ripretinib[5]

***Carcinogenicity:*** Carcinogenicity studies have not been conducted. New primary malignancies have been reported with ripretinib.[4,5]

***Mutagenicity:*** Not mutagenic in Ames test. Ripretinib is not clastogenic in mammalian *in vivo* chromosome test.[4,5]

***Fertility:*** In animal studies, bilateral degeneration of the testes and increased cellular debris of the epididymis were observed at exposures approximately 0.5 times those seen following human clinical exposure. Testicular and epididymal weights were correspondingly decreased. Effects were not reversible. Sperm preservation is recommended for patients prior to starting treatment.[4,5]

***Pregnancy:*** In animal studies, ripretinib caused embryo-fetal developmental toxicity. Malformations associated with the cardiovascular and skeletal systems (as well as anatomic variations) were observed at exposures approximately 0.5 times those seen following human clinical exposure. Decreased fetal body weights and post-implantation loss were observed at exposures approximately 2 times those seen following human clinical exposure. Total loss of pregnancy occurred at doses approximately 3.5 times those seen following human clinical exposure. Pregnancy tests are recommended for female patients of childbearing potential prior to starting treatment. Contraception is recommended for female patients of childbearing potential and male patients with female partners of childbearing potential. Contraception should be used starting two weeks before treatment, and continue through treatment until at least one complete uterine cycle past the last dose of ripretinib.[4,5]

***Breastfeeding*** is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for two weeks following the last dose of ripretinib.[4,5]

## 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.[6,7] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[2]

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia | anemia (4-14%, severe 9%) |
| | neutropenia (10%) |


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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| cardiac | ***cardiac dysfunction***, including cardiac failure, diastolic dysfunction, and ventricular hypertrophy (3%, severe 1%) |
| | ***cardiac ischemic event***, including cardiac arrest, myocardial infarction, acute coronary syndrome (1%); fatal events reported |
| eye | blurred vision (<10%) |
| gastrointestinal | *emetogenic potential:* low[8] |
| | abdominal distention (<10%) |
| | ***abdominal pain*** (36-37%, severe 7%) |
| | constipation (34%, severe 1%) |
| | diarrhea (28%, severe 1%) |
| | dyspepsia (<10%) |
| | fecaloma (1%) |
| | flatulence (<10%) |
| | gastroesophageal reflux disease (1%) |
| | gingival bleeding (<10%) |
| | ***nausea*** (39%, severe 4%) |
| | stomatitis (11%) |
| | ***vomiting*** (21%, severe 4%) |
| | upper gastrointestinal hemorrhage (1%) |
| general disorders and administration site conditions | asthenia (13%, severe 1%) |
| | ***fatigue*** (42%, severe 4%) |
| | peripheral edema (17%, severe 1%) |
| | pyrexia (<10%) |
| immune system | hypersensitivity (<10%) |
| infections and infestations | upper respiratory tract infection (<10%) |
| | urinary tract infection (<10%) |
| investigations | activated partial thromboplastin time increase (35%) |
| | alkaline phosphatase increase (<10%) |
| | ALT increase (12%, severe 1%) |
| | amylase increase (13%, severe 1%) |
| | AST increase (<10%) |
| | bilirubin increase (17-22%, severe <1%) |
| | calcium decrease (23%) |
| | CPK increase (21%, severe 1%) |
| | creatinine increase (16%) |


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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| | ***ejection fraction decrease*** (severe 3%) |
| | INR increase (21%, severe 4%) |
| | lipase increase (11-32%, severe 5-7%) |
| | triglycerides increase (26%, severe 2%) |
| | weight decrease (19%) |
| metabolism and nutrition | ***appetite decrease*** (27%, severe 1%) |
| | dehydration (<10%) |
| | hyperglycemia (<10%) |
| | hypomagnesemia (<10%) |
| | hyponatremia (17%, severe 2%) |
| | hypophosphatasemia (11-26%, severe 5%) |
| musculoskeletal and connective tissue | arthralgia (18%) |
| | arthritis (severe 1%) |
| | muscle spasms (15%) |
| | musculoskeletal pain (<10%) |
| | ***myalgia*** (32%, severe 1%) |
| neoplasms | benign neoplasms of skin (<10%) |
| | ***keratocanthoma*** (2%) |
| | ***melanoma*** (1-3%) |
| | ***squamous cell carcinoma*** (5-7%); median time to onset is 4.6 months |
| nervous system | agitation (severe 1%) |
| | dysgeusia (<10%) |
| | ***headache*** (19%) |
| | hyperesthesia (severe 1%) |
| | peripheral sensory neuropathy (<10%) |
| psychiatric | anxiety (<10%) |
| | depression (<10%) |
| | insomnia (<10%) |
| respiratory, thoracic and mediastinal | dyspnea (13%) |
| skin and subcutaneous tissue | actinic keratosis (6%) |
| | ***alopecia*** (52%) |
| | dry skin (13%) |
| | hyperkeratosis (<10%) |
| | maculopapular rash (<10%) |


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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| | ***palmar-plantar erythrodysesthesia syndrome*** (21%) |
| | ***photosensitivity reaction*** (<10%) |
| | pruritus (11%) |
| vascular | ***hypertension*** (14%, severe 7%) |

Adapted from standard reference[1,4,5] unless specified otherwise.

***Impaired would healing*** has been associated with medications that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. In patients undergoing minor and major surgical procedures, temporary interruption of ripretinib is recommended. Consider withholding ripretinib for a minimum of one week prior to elective surgery and for at least two weeks following major surgery. Restart ripretinib once adequate wound healing has occurred post-surgery.[4,5]

## INTERACTIONS:

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| efavirenz[4,5] | *predicted* 56% decrease in AUC and 24% decrease in $C_{max}$ of ripretinib; *predicted* 56% decrease in AUC and 7% decrease in $C_{max}$ of DP-5439 | moderate induction of CYP 3A4 by efavirenz | avoid concurrent use; if concurrent use cannot be avoided, increase ripretinib dose to 150 mg PO twice daily |
| itraconazole[4,5] | 99% increase in AUC and 36% increase in $C_{max}$ of ripretinib; 99% increase in AUC and 6% increase in $C_{max}$ of DP-5439 | strong inhibition of CYP 3A4 by itraconazole | monitor for ripretinib toxicity |
| pantoprazole[4,5] | no clinically significant difference in pharmacokinetics of ripretinib or DP-5439 | pH-dependent solubility of ripretinib | |
| rifampin[4,5] | 61% decrease in AUC and 18% decrease in $C_{max}$ of ripretinib; 57% decrease in AUC and 37% decrease in $C_{max}$ of DP-5439 | strong induction of CYP 3A4 by rifampin | avoid concurrent use; if concurrent use cannot be avoided, increase ripretinib dose to 150 mg PO twice daily |

Ripretinib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentration of ripretinib and its active metabolite. Grapefruit and grapefruit juice may increase the plasma level of ripretinb by inhibiting CYP 3A4 metabolism in the intestinal wall. Monitor for ripretinib toxicity if coadministration with CYP 3A4 inhibitors cannot be avoided. CYP 3A4 ***inducers*** may decrease the plasma concentration of ripretinib. Avoid concurrent use with *moderate* or *strong* CYP 3A4 inducers. If concurrent use with *moderate* or *strong* CYP 3A4 inducers cannot be avoided, increase ripretinib dose to 150mg PO twice daily. If the CYP 3A4 inducer is discontinued, ripretinib may be resumed at the prior dose after 14 days.[4,5]

Ripretinib is an inhibitor of CYP 2C8, P-gp, and BCRP *in vitro*. DP-5439 is an inhibitor of CYP 2C8, BCRP, and MATE1 and a substrate of BCRP and P-gp *in vitro*. Clinical significance is unknown.[4,5]


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## SUPPLY AND STORAGE:

***Oral:*** Deciphera Pharmaceuticals, LLC (distributor Medison Pharma Canada Inc.) supplies ripretinib as 50 mg tablets. Tablets contain lactose. Store at room temperature in original bottle with desiccant. Protect from light and moisture.[5,9]

***Additional information:*** Ripretinib did not pass the International Conference on Harmonisation (ICH) photostability requirements when exposed outside the closed original container. Dispense ripretinib in original bottle with desiccant.[9]

## 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:*[2,5,10,11] | ***150 mg*** (range 50-150 mg) ***PO once daily**** <br> May consider dose escalation to 150 mg BID.[2,10,11] <br><br> *twice daily dosing may be required for some drug interactions <br><br> Administer with food or on an empty stomach. |
| *Concurrent radiation:* | no information found |
| *Dosage in myelosuppression:* | modify according to protocol by which patient is being treated |
| *Dosage in renal failure:* | CrCl ≥30 mL/min: no adjustment required[5] <br> CrCl <30 mL/min: no information found <br><br> calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ <br><br> * For males N=1.23; for females N=1.04 |
| *Dosage in hepatic failure:* | mild impairment (total bilirubin ≤1 x ULN and AST >1 x ULN OR total bilirubin 1.0 to 1.5 x ULN): no adjustment required[5] <br> moderate/severe impairment: no information found |
| *Dosage in dialysis:* | no information found |

***Children:*** safety and efficacy have not been established[5]


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