Drug Monograph

A - Drug Name

ripretinib

COMMON TRADE NAME(S): Qinlock™

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B - Mechanism of Action and Pharmacokinetics

Ripretinib is a tyrosine kinase inhibitor. It inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and Platelet-Derived Growth Factor Receptor A (PDGFRA) kinase activity, including wild-type and multiple primary and secondary mutations. *In vitro*, ripretinib also inhibits PDGFRB, TIE2, VEGFR2, and BRAF.

Ripretinib has a dual mechanism of action. It binds to both the switch pocket and the activation loop, and locks the kinase in the inactive state, inhibiting downstream signaling and cell proliferation.

Absorption	Effects with food	Although a high-fat, high-calorie meal increased AUC by 30% and Cmax by 22%, these changes were not considered clinically relevant.
	T max	2 hours (median at steady state)
	Time to reach steady state	15 days
Distribution	PPB	99% (albumin and α-1 acid glycoprotein)
Metabolism	Ripretinib is primarily metabolized by CYP3A4/5 via N-dealkylation and oxidation pathways.	
	Active metabolites	Yes (DP-5439)

Elimination	Feces	34% (ripretinib); 6% (DP-5439)
	Urine	0.02% (ripretinib); 0.1% (DP-5439)
	Half-life	14.8 hours (ripretinib); 17.8 hours (DP-5439)

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C - Indications and Status

Health Canada Approvals:

- Gastrointestinal stromal tumor (GIST)

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 events were reported in ≥ 10% of patients with advanced GIST who were treated with ripretinib in a Phase 3 study. It also included severe or life-threatening adverse events from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiac ischemia (1%) (may be severe)	E
	Cardiotoxicity (1%)	E
	Ejection fraction decreased (3%) (severe)	E
	Hypertension (14%) (7% severe)	E
Dermatological	Alopecia (52%)	E D
	Dry skin (13%) (including pruritus)	E
	Hand-foot syndrome (21%)	E
	Photosensitivity (<10%)	E

Gastrointestinal	Abdominal pain (37%)	E
	Anorexia, weight loss (27%)	E
	Constipation (34%)	E
	Diarrhea (28%)	E
	Mucositis (11%)	E
	Nausea, vomiting (39%) (4% severe)	E
General	Delayed wound healing (observed with other VEGF inhibitors)	E
	Edema - limbs (17%)	E
	Fatigue (42%)	E
Hepatobiliary	↑ Bilirubin (17%)	E
	↑ Lipase (11%)	E
Hypersensitivity	Hypersensitivity (rare)	I E
Metabolic / Endocrine	↓ PO4 (11%)	E
Musculoskeletal	Musculoskeletal pain (32%)	E
Neoplastic	Secondary malignancy (5%) (SCC of the skin, melanoma)	D L
Nervous System	Headache (19%)	E
Respiratory	Dyspnea (13%)	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 ripretinib include alopecia, fatigue, nausea, vomiting, abdominal pain, constipation, musculoskeletal pain, diarrhea, anorexia, weight loss, hand-foot syndrome and headache.

Squamous cell carcinoma (SCC) of the skin was reported with a median onset of ~5 months. No dose reduction or interruption is required for **actinic keratosis** or **new primary cutaneous malignancies**.

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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.

Blood pressure should be adequately controlled prior to initiation of ripretinib. Hold ripretinib for at least 3 days prior to and after minor surgery and at least 5 days prior to and after major surgery. The decision to resume after surgery should be based on clinical judgment of adequate wound healing.

Other supportive care:

- Due to risk of photosensitivity, patients should avoid or minimize exposure to strong sunlight or other sources of UV radiation until at least 1 week after discontinuation of treatment. They should use a sunscreen and wear protective clothing to cover the skin when exposed to strong sunlight.

Adults:

Oral: 150 mg Daily

Dosage with Toxicity:

Dose Levels	Ripretinib Dose (mg daily)
0	150
-1	100
-2	Discontinue permanently.

Toxicity	Severity	Action
Hand-foot syndrome	Grade 2	Hold* for at least 7 days. If resolves within 7 days, resume at same dose level. If resolves after 7 days, resume at 1 dose level ↓. • Consider re-escalation if maintained at Grade 1 or baseline for at least 28 days. If recurs, hold*. Resume at 100 mg regardless of time to improvement.
	Grade 3	Hold* for at least 7 days (maximum 28 days). Resume at 1 dose level ↓. Consider re-escalation if maintained at Grade 1 or baseline for at least 28 days.
Hypertension	Grade 3	Medically manage to achieve ≤ Grade 1. If symptomatic, hold until symptoms resolve. • If blood pressure is controlled to ≤ Grade 1, resume at the same dose; otherwise, resume at 1 dose level ↓. If recurs despite dose modification and medical management, discontinue.
	Grade 4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Discontinue.
Arthralgia, myalgia	Grade 2	Hold* for at least 7 days. If resolves within 7 days, resume at same dose level. If resolves after 7 days, resume at 1 dose level ↓. • Consider re-escalation if maintained at Grade 1 or baseline for at least 28 days. If recurs, hold*. Resume at reduced dose level (i.e. 100 mg) regardless of time to improvement.

	Grade 3	Hold* for at least 7 days (maximum 28 days). Resume at 1 dose level ↓; otherwise, discontinue. Consider re-escalation if maintained at Grade 1 or baseline for at least 28 days.
Left ventricular systolic dysfunction	Grade 3 or 4	Discontinue
Isolated Bilirubin Increased	Grade 2	Hold* (maximum 28 days). Restart with 1 dose level ↓.
	Grade 3 or 4	See "Other toxicities" below.
Actinic keratosis	Any	No dose modification required. Patients with suspicious skin lesions should be referred for evaluation immediately.
New primary cutaneous malignancies		
Other toxicities	Grade 3 or 4	Hold* (maximum 28 days), then resume at 1 dose level ↓; otherwise, discontinue. Consider re-escalation if maintained at Grade 1 or baseline for at least 28 days. Discontinue at recurrence.

*Do not resume until hand-foot syndrome, musculoskeletal pain, increased bilirubin, or other toxicities resolve to Grade 1 or baseline.

Dosage with Hepatic Impairment:

No dose adjustment is recommended in patients with hepatic impairment (Child-Pugh A, B or C).

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Ripretinib Dose
≥ 30	No dose adjustment required
< 30	Not studied

Dosage in the elderly:

No dose adjustment required in patients of ≥ 65 years of age. Although data are limited, no differences in safety or efficacy were observed between patients ≥ 65 years of age and patients < 65 years.

Dosage based on gender:

Sex does not appear to have a clinically relevant effect on the pharmacokinetics of ripretinib.

Dosage based on ethnicity:

Ethnicity does not have a clinically meaningful effect on the pharmacokinetics of ripretinib.

Children:

The safety and efficacy of ripretinib in children < 18 years have not been established. Alterations of teeth and bones/cartilage were documented in animal studies and may indicate a potential risk for children < 18 years.

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F - Administration Guidelines

- Ripretinib may be taken with or without food at about the same time each day.
- Tablets should be swallowed whole and not chewed, split, or crushed.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during ripretinib treatment
- **For patients taking 150 mg once daily (standard dose):** if a dose is missed, patient may take within 8 hours of missed dose. If more than 8 hours, the dose should be skipped and taken at the next planned time. Extra doses should not be taken to make up for missed dose.
- **For patients taking 150 mg twice daily (with strong or moderate CYP3A4 inducers):** if a dose is missed, patient may take within 4 hours of missed dose. If more than 4 hours, the dose should be skipped and taken at the next planned time. Extra doses should not be taken to make up for missed dose.
- If 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°C to 25°C) in the original container.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any of its components

Other Warnings/Precautions:

- Use caution and monitor more frequently in patients who have experienced hypersensitivity with prior use of other tyrosine kinase inhibitors.
- Patients with a baseline LVEF < 50%, CrCl < 50 mL/min, creatinine > 1.5 x ULN, or bilirubin > 1.5 x ULN and/or AST > 3 x ULN (> 5 x ULN with hepatic metastases) were excluded from clinical trials. Consider the benefits vs risks of using ripretinib in these patients.

Other Drug Properties:

- Carcinogenicity: No information available
- Phototoxicity: Documented in humans

Pregnancy and Lactation:

- Mutagenicity:
  Not observed in *in vitro* or *in vivo* assays
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Pregnancy:
  Ripretinib is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners starting 2 weeks before treatment, during treatment, and for at least **1 complete uterine cycle** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners starting 2 weeks before treatment, during treatment, and for at least **1 complete uterine cycle** (of the partner) after the last dose.
  - It is not known if ripretinib can affect hormonal contraception. If a hormonal contraception method must be used, a barrier method of contraception (e.g. condoms) must be used together with the hormonal contraception.
- Breastfeeding:
  Breastfeeding is not recommended during treatment, and for at least **2 weeks** after the last dose.
- Fertility effects:
  Documented in studies with male animals. Discuss fertility preservation with patients prior to starting treatment.

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H - Interactions

CYP3A4/5 is the major metabolizer of ripretinib. Coadministration of strong CYP3A inhibitors or inducers affected the exposure to ripretinib and DP-5439.

Ripretinib and DP-5439 are likely to inhibit CYP2C8. Ripretinib is not an inducer of CYP1A2, CYP2B6, and CYP3A4.

Ripretinib is an inhibitor of P-gp and BCRP. DP-5439 is an inhibitor of BCRP and MATE1. In addition, DP-5439 is a substrate for P-gp and BCRP.

No clinically significant differences in exposure to ripretinib were observed when coadministered with pantoprazole.

Effects of ripretinib on **hormonal contraceptives** have not been studied. A barrier method of contraception (e.g. condoms) should be added if hormonal contraceptives are used.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A inhibitors (e.g. ketoconazole, itraconazole)	↑ ripretinib exposure (↑ AUC by 99% with itraconazole)	↓ metabolism of ripretinib	Caution; monitor ripretinib toxicities closely.
Grapefruit juice	↑ ripretinib exposure	↓ metabolism of ripretinib	Caution; monitor ripretinib toxicities closely.
Strong and moderate CYP3A4 inducers (e.g. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ ripretinib exposure (↓ AUC by 61% with rifampin)	↑ metabolism of ripretinib	Avoid concomitant use with strong or moderate CYP3A inducers. If must use a strong or moderate inducer, increase ripretinib dose to 150 mg twice daily. If inducer is discontinued, decrease ripretinib dose to previous dose 14 days after discontinuation of inducer.

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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
CBC	Baseline, monthly, and as clinically indicated
Liver function tests	Baseline, monthly, and as clinically indicated
Renal function tests	Baseline, monthly, and as clinically indicated
Blood pressure	Baseline, monthly, and as clinically indicated
LVEF (ECG or MUGA scan)	Baseline and as clinically indicated
Skin assessment (for new primary cutaneous malignancies)	Baseline and as clinically indicated
Clinical toxicity assessment for hypersensitivity, delayed wound healing (if applicable), musculoskeletal, gastrointestinal, cardiovascular, and skin effects	At each visit

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)

- ripretinib - For adult patients with advanced gastrointestinal stromal tumours (GIST) who have progression on or intolerance to imatinib, sunitinib and regorafenib

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K - References

Blay J-Y, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020 Jul;21(7):923-34.

CADTH reimbursement recommendation: ripretinib (advanced gastrointestinal stromal tumour). May 2022.

NCCN Guidelines. Antiemesis. May 24, 2023.

Prescribing Information: QINLOCK® (ripretinib) tablets, for oral use. Deciphera Pharmaceuticals, LLC. December 2022.

Product Monograph: Qinlock (ripretinib). Deciphera Pharmaceuticals, LLC. July 9, 2024.

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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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