PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**QINLOCK™**

ripretinib tablets

Tablets, 50 mg, Oral

Antineoplastic Agent

Deciphera Pharmaceuticals, LLC
200 Smith Street,
Waltham, MA 02451
United States

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	05/2022
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

QINLOCK™ (ripretinib) is indicated for:

- the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use [see WARNINGS AND PRECAUTIONS, Special Populations].

1.2 Geriatrics

Geriatrics (≥65 years of age): There are limited clinical data in patients aged 65 years and over. Although data are limited, no clinically important differences in safety or efficacy were observed between patients 65 years of age or older and patients under 65 years [see WARNINGS AND PRECAUTIONS, Special Populations].

2 CONTRAINDICATIONS

QINLOCK is contraindicated in patients who are hypersensitive to ripretinib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The following are clinically significant adverse events:

- Cardiac Dysfunction (see WARNINGS AND PRECAUTIONS - Cardiovascular)
- Hypertension (see WARNINGS AND PRECAUTIONS – Cardiovascular)
- New Primary Cutaneous Malignancies – Squamous Cell Carcinoma and Melanoma (see WARNINGS AND PRECAUTIONS – Skin)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- QINLOCK dose modification is recommended based on individual tolerability. Management of some adverse reactions may require dose interruption, dose reduction, or discontinuation [see Recommended Dose and Dosage Adjustment].

- Concomitant use with a strong CYP3A inhibitor increases plasma ripretinib concentrations. Monitor patients more frequently for adverse reactions if QINLOCK is given concurrently with a strong CYP3A inhibitor [see DRUG INTERACTIONS].
- Avoid concomitant strong or moderate CYP3A inducers during QINLOCK treatment. If a strong or moderate CYP3A inducer must be co-administered, increase the QINLOCK dosing frequency from the recommended dose of 150 mg once daily to 150 mg twice daily during the co-administration period. Monitor for clinical response and tolerability. If the concomitant strong or moderate CYP3A inducer is discontinued, resume QINLOCK dosage back to 150 mg once daily 14 days after the discontinuation of the CYP3A inducer [see DRUG INTERACTIONS].

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dose of QINLOCK is 150 mg (three 50 mg tablets) taken orally once daily.

Dosage Adjustment

The recommended dose reduction for adverse reactions is:

- QINLOCK 100 mg orally once daily

Permanently discontinue QINLOCK in patients who are unable to tolerate 100 mg orally once daily.

The recommended dosage modifications of QINLOCK for adverse reactions are provided in Table 1.

Table 1: Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modifications
Palmar-plantar erythrodysesthesia syndrome [PPES]*	Grade 2	• Interrupt QINLOCK for at least 7 days. • If the event returns to Grade 1 or baseline within 7 days, resume QINLOCK at the same dose level. • If the event returns to Grade 1 or baseline after 7 days, resume QINLOCK at 100 mg. • If after dose reduction, the event is maintained at Grade 1 or baseline for at least 28 days, consider re-escalating QINLOCK. • If this is a recurrence, after event returns to Grade 1 or baseline, resume QINLOCK at 100 mg regardless of time to improvement.
	Grade 3	• Interrupt QINLOCK for at least 7 days (maximum 28 days). Resume QINLOCK at 100 mg when events return to Grade 1 or baseline. • If after dose reduction the event is maintained at Grade 1 or baseline for at least 28 days of dosing, consider

Adverse Reaction	Severity[a]	Dosage Modifications
		re-escalating QINLOCK.
Hypertension	Grade 3	• Medically manage hypertension to achieve Grade 1 or lower blood pressure. • If symptomatic hypertension, withhold QINLOCK until hypertension has resolved to Grade 1 or less and symptoms have resolved. Resume QINLOCK at the same dose level after symptoms have resolved and hypertension has resolved to Grade 1 or less. • If blood pressure is not controlled to Grade 1 or less but symptoms have resolved with medical management, reduce QINLOCK dose to 100 mg. • If Grade 3 hypertension recurs despite QINLOCK dose reduction and medical management, discontinue QINLOCK
	Grade 4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	• Discontinue QINLOCK permanently.
Arthralgia or Myalgia*	Grade 2	• Interrupt QINLOCK for at least 7 days. • If the event returns to Grade 1 or baseline within 7 days, resume QINLOCK at the same dose level. • If the event returns to Grade 1 or baseline after 7 days, resume QINLOCK at 100 mg. • If after dose reduction, the event is maintained at Grade 1 or baseline for at least 28 days of dosing, consider re-escalating QINLOCK. If this is a recurrence, after event returns to Grade 1 or baseline, resume QINLOCK at 100 mg regardless of time to improvement.
	Grade 3	• Interrupt QINLOCK for at least 7 days (maximum 28 days). Resume QINLOCK at 100 mg when event returns to Grade 1 or baseline; otherwise permanently discontinue QINLOCK. • If after dose reduction the event is maintained at Grade 1 or baseline for at least 28 days of dosing, consider re-escalating QINLOCK

Adverse Reaction	Severity[a]	Dosage Modifications
Left Ventricular Systolic Dysfunction	Grade 3 or 4	• Discontinue QINLOCK permanently
Isolated Bilirubin Increased	Grade 2	• Interrupt QINLOCK until toxicity resolves to Grade 1 or baseline (maximum 28 days); resume QINLOCK at 100 mg.
	Grade 3 or 4	• See other adverse reactions
Other adverse reactions	Grade 3 or 4	• Interrupt QINLOCK until toxicity resolves to Grade 1 or baseline (maximum 28 days); otherwise permanently discontinue QINLOCK. • If the event returns to Grade 1 or baseline, resume QINLOCK at 100 mg. • If the reduced dose is tolerated without recurrence of the event for at least 28 days, consider re-escalating QINLOCK. • If Grade 3 or higher toxicity recurs, discontinue QINLOCK permanently.
[a] Graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03). * Grade 4 events for Palmar-Plantar Erythrodysaesthesia Syndrome (PPES) and Arthralgia or myalgia does not exist in CTCAE		

Dose Modifications for CYP3A Inducers

Avoid concomitant strong or moderate CYP3A inducers during QINLOCK treatment.

If a strong or moderate CYP3A inducer must be co-administered, increase the QINLOCK dosing frequency from the recommended dose of 150 mg once daily to 150 mg twice daily during the co-administration period. Monitor for clinical response and tolerability. If the concomitant strong or moderate CYP3A inducer is discontinued, resume QINLOCK dosage back to 150 mg once daily 14 days after the discontinuation of the CYP3A inducer [see DRUG INTERACTIONS].

Special Populations

Pediatrics (<18 years old): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years old): No dose adjustment is required in patients of ≥65 years of age [see ACTION AND CLINICAL PHARMACOLOGY].

Renal impairment: No dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance (CrCl) 30 to 89 mL/min estimated by Cockcroft-Gault].

The pharmacokinetics and safety of QINLOCK in patients with end-stage renal disease (CrCl <15mL/min estimated by Cockcroft-Gault or requiring dialysis) or severe renal impairment (CrCl 15 to 29 mL/min) have not been studied [see ACTION AND CLINICAL PHARMACOLOGY].

Hepatic impairment: No dose adjustment is recommended in patients with hepatic impairment (Child-Pugh A, B or C) [See ACTION AND CLINICAL PHARMACOLOGY].

4.4 Administration

QINLOCK may be taken with or without food. Patients should be instructed to swallow tablets whole and not to chew, split, or crush tablets. Patients should not ingest if tablets are broken, cracked, or otherwise not intact. QINLOCK should be taken at the same time each day.

4.5 Missed Dose

For patients taking 150 mg once daily: If the patient misses a dose or has not taken the dose at the usual time, the patient should take the dose within 8 hours of the scheduled time that was missed. If more than 8 hours have passed since the time the dose is usually taken, the patient should not take the missed dose and should resume the dosing schedule the next day at the usual time.

For patients taking 150 mg twice daily: if the patient misses a dose within 4 hours of the time it is usually taken, advise the patient to take the missed dose as soon as possible and then take the next dose at the regularly scheduled time. If a patient misses a dose by more than 4 hours of the time it is usually taken, advice the patient to skip the missed dose and simply resume the usual dosing schedule

If the patient vomits after taking a dose, the patient should not take a replacement dose and should resume the dosing schedule the next day at the usual time.

5 OVERDOSAGE

There is no known specific antidote for QINLOCK overdose. In the event of suspected overdose, interrupt QINLOCK, undertake general supportive measures, and observe until clinical stabilization.

For management of a suspected drug overdose, contact your regional poison control center.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	50 mg ripretinib tablet	crospovidone, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and silicon dioxide.

50 mg tablets of QINLOCK are white to off-white oval tablet debossed with 'DC1' on one side of the tablet; available in bottles of 90 tablets.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part 1: Health Professional Information.

Carcinogenesis and Mutagenesis

New Primary Cutaneous Malignancies

Squamous cell carcinoma (SCC) of the skin was reported in 4.7% of the 85 patients who received QINLOCK in INVICTUS, with a median time to event of 4.6 months (range: 3.8 to 6 months). SCC of the skin was not reported in placebo-treated patients.

Melanoma occurred in 2.4% of patients in the ripretinib treatment arm and none in the placebo treatment arm in INVICTUS. In the pooled safety population, melanoma occurred in 0.9% of 351 patients.

Cardiovascular:

Cardiac dysfunction

In the double-blind period of the randomized, placebo-controlled phase 3 pivotal study in patients with GIST (INVICTUS), cardiac failure occurred in 1.2% of the 85 patients who received QINLOCK. Grade 3 decreased ejection fraction occurred in 2.6% of the 77 patients who received QINLOCK and who had a baseline and at least one post-baseline echocardiogram. Cardiac dysfunction led to a dose discontinuation in 1.2% of patients.

In the pooled safety population of 351 patients, cardiac dysfunction occurred in 1.7% of patients including grade 3 adverse reactions in 1.1% of patients. Grade 3 decreased ejection fraction occurred in 3.4% of the 263 patients who received QINLOCK and who had a baseline and at least one-post baseline echocardiogram.

The safety of QINLOCK has not been assessed in patients with a baseline ejection fraction below 50% as they have been excluded from the INVICTUS study.

Permanently discontinue QINLOCK for Grade 3 or 4 left ventricular systolic dysfunction.

Cardiac Ischemic Events

In the pooled safety population, cardiac ischemic events (cardiac arrest, acute coronary syndrome, and myocardial infarction), occurred in 1.1% of patients. Of these, cardiac arrest and myocardial infarction were reported as fatal adverse reactions.

Hypertension

In INVICTUS, there was a higher incidence of hypertension in patients treated with QINLOCK (14.1% in QINLOCK-treated patients vs. 4.7% of placebo-treated patients). Grade 3 hypertension was reported in 7.1% of QINLOCK-treated patients [see ADVERSE REACTIONS].

Immune:

Hypersensitivity

In a supportive clinical study, an event of hypersensitivity occurred in a QINLOCK treated patient who also had a similar reaction with another tyrosine kinase inhibitor. Exercise precaution and more frequent monitoring for hypersensitivity symptoms in patients who have experienced a hypersensitivity in association with prior use of other tyrosine kinase inhibitors.

Monitoring and Laboratory Tests

An assessment of the ejection fraction by echocardiogram or MUGA scan is recommended prior to initiation of QINLOCK and during treatment with QINLOCK, as clinically indicated.

Do not initiate QINLOCK in patients with uncontrolled hypertension. Adequately control blood pressure prior to initiating QINLOCK. Monitor blood pressure as clinically indicated during treatment with QINLOCK and initiate or adjust antihypertensive therapy as appropriate.

Dermatological assessment should be performed when initiating QINLOCK and patients should

receive dermatological examinations routinely. Patients should be advised to inform their physician if any skin lesions develop, change or worsen. It is recommended to manage suspicious skin lesions with biopsy and/or excision with a dermatopathological evaluation.

Peri-Operative Considerations:

Wound Healing

Impaired wound healing complications can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, QINLOCK has the potential to adversely affect wound healing.

No formal trials to evaluate the effect of QINLOCK on wound healing have been conducted. Treatment with QINLOCK is to be withheld 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 QINLOCK after surgery should be based on clinical judgment of adequate wound healing.

Reproductive Health: Female and Male Potential

Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception to commence 2 weeks prior to treatment, during treatment and for at least one complete uterine cycle after the final dose of QINLOCK. Effects of QINLOCK on contraceptive steroids have not been studied. A barrier method contraception should be added if systemic contraceptive steroids are used. [see Special Populations, Pregnant Women].

Fertility

Fertility studies have not been conducted with QINLOCK. Based on findings from animal studies, QINLOCK has the potential to impair fertility in males of reproductive potential at exposures similar to human clinical exposures. It is recommended to advise male patients on sperm preservation prior to initiating therapy. [see NON-CLINICAL TOXICOLOGY].

Teratogenic Risk

Female patients of reproductive potential should be tested for pregnancy prior to initiating therapy.

Based on findings from animal studies, QINLOCK can cause fetal harm when administered to pregnant women. Advise women to avoid pregnancy while taking QINLOCK.

There are no clinical data on the use of QINLOCK in pregnant women. Ripretinib was teratogenic in pregnant rats and resulted in malformations primarily associated with the cardiovascular and skeletal systems, anatomic variations, and decreased fetal body weight and post implantation loss at doses of 20 mg/kg/day (approximately one half of the human exposure at 150 mg once daily) [see NON-CLINICAL TOXICOLOGY]. QINLOCK should not be used in pregnant women. If the patient becomes pregnant while receiving QINLOCK, the patient should discontinue treatment.

Skin:

Palmar-Plantar Erythrodysesthesia Syndrome

Mild to moderate palmar-plantar erythrodysesthesia syndrome [PPES] occurred in patients treated with QINLOCK. PPES occurred in 21.2% of QINLOCK-treated patients and were Grade 1-2 in severity (Grade 1 was 12.9%). PPES was not observed in placebo-treated patients [see ADVERSE REACTIONS].

PPES led to dose discontinuation in 1.2% of patients, dose interruption in 2.4% of patients, and dose reduction in 1.2% of patients.

Temporarily hold, reduce, or discontinue QINLOCK depending on the type, severity and persistence of the dermatologic toxicity [see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment]. Consider topical treatment based on the severity of the dermatologic toxicity and as a preventative measure.

Actinic Keratosis

Actinic keratosis was reported in 5.9% of patients receiving QINLOCK and 2.3% receiving placebo in INVICTUS. In the pooled safety population, 1.9% of patients receiving QINLOCK reported an adverse event of keratoacanthoma.

No dose reduction or interruption is required for actinic keratosis or new primary cutaneous malignancies.

Photosensitivity

QINLOCK is potentially phototoxic (see NON-CLINICAL, Special Toxicology Studies). Exposure to strong sunlight, sunlamps, and other sources of ultraviolet radiation should be avoided or minimized while taking QINLOCK and for at least one week after discontinuation of treatment.

7.1 Special Populations

7.1.1 Pregnant Women

Based on findings from animal studies [see NON-CLINICAL TOXICOLOGY], QINLOCK can cause embryo-fetal harm when administered to a pregnant woman. There are no clinical data on the use of QINLOCK in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In an animal reproduction study, administration of ripretinib to pregnant rats during organogenesis resulted in malformations primarily associated with the cardiovascular and skeletal systems at a dose of 20 mg/kg/day. Additional indications of developmental toxicity at this dose included anatomic variations, reduced fetal body weight and post implantation loss [see NON-CLINICAL TOXICOLOGY]. QINLOCK should not be administered to pregnant women.

7.1.2 Breast-feeding

There is no information regarding the presence of ripretinib or its metabolites in human milk or their effects on the breastfed infant or on milk production. Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment and for at least 2 weeks after the final dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of QINLOCK in children and adolescents aged less than 18 years have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Although no dedicated studies in juvenile animals were performed, toxicology studies in rodents showed increased osteoblastic surface and/or decreased trabecular in the femur and degeneration of growing incisors. Alterations of teeth and bones/cartilage may indicate a potential risk for children and adolescents.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Of the 85 patients in INVICTUS Study who received 150 mg QINLOCK orally once daily, 23.5% were between 65 to 74 years of age and 9.4% were 75 years of age or older. Although data are limited, no clinically important differences in safety or efficacy were observed between patients 65 years of age or older and patients under 65 years [see ACTION AND CLINICAL PHARMACOLOGY].

Renal impairment

Patients with CrCl of <50 ml/min or a creatinine above 1.5 x upper limit of normal were excluded from the INVICTUS study.

Hepatic impairment

Patients with a total bilirubin above 1.5 x the ULN and/or an aspartate transaminase (AST) above 3 x ULN (>5 x ULN if the patient has the presence of hepatic metastases) were excluded from the INVICTUS Study.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In the Phase 3 double-blind, randomized (2:1), placebo-controlled trial (INVICTUS), 129 study participants with a diagnosis of advanced GIST received QINLOCK (N=85) or placebo (N=44) [see CLINICAL TRIALS]. One study participant randomized to the placebo arm did not receive treatment. The data described in this section reflect the safety population (N=128) who had received at least one dose of QINLOCK (N=85) or placebo (N=43). Patient characteristics of the safety population include a median age of 59.5 years (29 to 83 years), age 18-64 years (61.7%), male (56.3%), White (75%), and Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42.2%), 1 (49.2%), or 2 (8.6%). The safety results described below are from the double-blind treatment period of INVICTUS. The median duration of exposure to QINLOCK was 23.9 weeks (1.3 to 59.4 weeks) and 45.9% received QINLOCK for ≥6 months.

The most common adverse events (≥20%) observed in patients treated with QINLOCK (all grades) in the Phase 3 double-blind, randomized placebo-controlled trial (INVICTUS) were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia syndrome, and vomiting.

Serious adverse events occurred in 31% of patients who received QINLOCK. Serious adverse reactions that occurred in >2% of patients were abdominal pain (4.7%), anemia (3.5%), nausea (2.4%), vomiting (2.4%). Serious adverse events considered to be drug-related were reported in one (1.2%) patient each: anemia, cardiac failure, death, dyspnea, fecaloma, gastroesophageal reflux disease, hyperkaliemia, hypophosphatasemia, nausea, and upper gastrointestinal hemorrhage.

Table 3: Dose Interruptions, Dose Reductions and Treatment Discontinuations due to Adverse Events

Event	QINLOCK (N=85) %	Placebo (N=43) %
Dose interruption	23.5	20.9
Dose reduction	7.1	2.3
Treatment discontinuation	8.2	11.6

In the double-blind treatment period of the INVICTUS Study:

Dosage interruptions due to an adverse event occurred in 23.5% of patients who received QINLOCK. Adverse events requiring dosage interruption in >2% of patients included nausea (3.5%), increased blood bilirubin (2.4%), and PPES (2.4%).

Dose reductions due to an adverse event occurred in 7.1% of patients who received QINLOCK. Adverse events resulting in a dose reduction in ≥1.2% of patients were abdominal pain, agitation, alopecia, arthritis, dermatosis, gastrointestinal disorder, hyperesthesia, myalgia, PPES, and decreased weight.

Permanent discontinuation due to an adverse event occurred in 8.2% of patients who received QINLOCK. Adverse events resulting in permanent discontinuation in ≥1% of patients included general physical health deterioration (2.4%), anemia (1.2%), cardiac failure (1.2%), PPES (1.2%), and vomiting (1.2%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described in this section reflect the safety population (N=128) who had received at least one dose of QINLOCK (N=85) or placebo (N=43). The safety results from the double-blind period of INVICTUS are described below.

Table 4 summarizes the most frequently reported treatment-emergent adverse events in ≥10% of patients with advanced GIST who received QINLOCK in the double-blind treatment period of INVICTUS.

Table 4: Treatment-Emergent Adverse Events Reported in ≥10% of Patients Who Received QINLOCK in the Double-Blind Treatment Period of INVICTUS[a]

	QINLOCK (N=85)		Placebo (N=43)	
Adverse Events	**All Grades (%)**	**Grade 3-5 (%)**	**All Grades (%)**	**Grade 3-5 (%)**
Any Adverse Event	99	53	98	51
Blood and lymphatic system disorders				
Anemia	14	9	19	14
Gastrointestinal disorders				
Nausea	39	3.5	12	0
Abdominal pain	37	7	30	7
Constipation	34	1.2	19	0
Diarrhea	28	1.2	14	2.3
Vomiting	21	3.5	7	0
Stomatitis	11	0	0	0
General disorders and administration site conditions				

	QINLOCK (N=85)		Placebo (N=43)	
Adverse Events	**All Grades (%)**	**Grade 3-5 (%)**	**All Grades (%)**	**Grade 3-5 (%)**
Fatigue	42	3.5	23	2.3
Peripheral edema	17	1.2	7	0
Asthenia	13	1.2	14	4.7
Investigations				
Weight decreased	19	0	12	0
Blood bilirubin increased	17	1.2	0	0
Lipase increased	11	4.7	0	0
Metabolism and nutrition disorders				
Decreased appetite	27	1.2	21	2.3
Hypophosphatasemia	11	4.7	0	0
Musculoskeletal and connective tissue disorders				
Myalgia	32	1.2	12	0
Arthralgia	18	0	4.7	0
Muscle spasms	15	0	4.7	0
Nervous system disorders				
Headache	19	0	4.7	0
Respiratory, thoracic and mediastinal disorders				
Dyspnea	13	0	0	0
Skin and subcutaneous tissue disorders				
Alopecia	52	0	4.7	0
Palmar-plantar erythrodysesthesia syndrome	21	0	0	0
Dry skin	13	0	7	0
Pruritus	11	0	4.7	0
Vascular disorders				
Hypertension	14	7	4.7	0

[a.] Adverse events graded according to National Cancer Institute Common Toxicity for Adverse Events version 4.03 (NCI CTCAE v4.03).

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse drug reactions have been reported in <10% of QINLOCK-treated patients in the pooled safety population which included 351 patients:

Cardiac disorders: Cardiac failure, cardiac ischemic event
Eye disorders: Vision blurred

Gastrointestinal disorders: Dyspepsia, gingival bleeding, flatulence, abdominal distention
General disorders and administration site conditions: Pyrexia, death
Immune system disorders: Hypersensitivity
Infections and infestations: Upper respiratory tract infection, urinary tact infection
Investigations: Aspartate aminotransferase increased**,** blood alkaline phosphatase increased
Metabolism and nutrition disorders: Hyponatremia, dehydration, hypomagnesemia, hyperglycemia
Musculoskeletal and connective tissue disorders: musculoskeletal pain
Neoplasms benign, malignant and unspecified (incl cysts and polyps): Benign neoplasms of skin, squamous cell carcinoma of skin, melanoma, keratoacanthoma
Nervous system disorders: Dysgeusia, peripheral sensory neuropathy
Psychiatric disorders: Insomnia, anxiety, depression
Skin and subcutaneous tissue disorders: Dermatitis acneiform, actinic keratosis, hyperkeratosis, seborrheic keratosis, skin papilloma, melanocytic naevus, rash, rash maculopapular, photosensitivity reaction

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 5 summarizes the most frequently reported treatment-emergent laboratory abnormalities in ≥10% of patients with advanced GIST who received QINLOCK in the double-blind treatment period of INVICTUS.

Table 5: Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Gastrointestinal Stromal Tumor Who Received QINLOCK with a Difference Between Arms of >5% Compared to Placebo in INVICTUS

Laboratory Abnormality	QINLOCK[a] (N=85)		Placebo[a] (N=43)	
	Grades 1-4	Grades 3/4[b]	Grades 1-4	Grades 3/4
Hematology/Coagulation				
Activated partial thromboplastin time increased	35	0	9	0
INR increased	21	3.8	15	0
Neutrophil count decreased	10	0	2.5	0
Chemistry				
ALT increased	12	1.2	5	0
Blood bilirubin increased	22	0	5	2.5
Calcium decreased	23	0	8	0
CPK increased	21	1.2	10	0
Creatinine increased	16	0	18	0
Lipase increased	32	7	13	8
Phosphate decreased	26	4.9	2.5	0
Serum amylase increased	13	1.2	5	0
Sodium decreased	17	2.4	10	2.5
Triglycerides increased	26	2.4	23	0
CPK=creatine phosphokinase; INR=international normalized ratio; AST=aspartate				

aminotransferase; ALT=alanine aminotransferase

a. The denominator used to calculate the rate varied from 82 to 83 for QINLOCK and 34 to 40 for placebo based on the number of patients with a baseline value and at least one post-treatment value.

b. Only includes Grade 3 laboratory abnormalities.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro data suggested that CYP3A4/5 is the major metabolizer of ripretinib. Potential interactions may occur with drugs/foods/herbs that are inhibitors or inducers of this enzyme system.

Coadministration of QINLOCK with strong cytochrome P450 (CYP)3A inhibitors increases exposure to ripretinib and its active metabolite (DP-5439), which may increase the risk of adverse reactions. Monitor patients more frequently for adverse reactions if QINLOCK is given concurrently with a strong CYP3A inhibitor [see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY].

Coadministration of QINLOCK with a strong CYP3A inducer decreased the exposure of ripretinib and its active metabolite (DP-5439). Coadministration of QINLOCK with moderate CYP3A inducers was predicted to decrease the exposure of ripretinib and its active metabolite, which may decrease QINLOCK anti-tumor activity.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, model-informed approaches, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Strong CYP3A Inhibitor (e.g., ketoconazole, itraconazole)	• CT	• Co-administration of itraconazole with a single 50 mg dose of ripretinib increased ripretinib $AUC_{0\text{-}INF}$ by 99% and C_{max} by 36% and also increased DP-5439 $AUC_{0\text{-}INF}$ by 99% and C_{max} by 6%	• Monitor patients more frequently for adverse reactions.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Strong and Moderate CYP3A Inducers	• CT • Model-informed approach	• Co-administration of rifampin with a single dose of ripretinib decreased ripretinib C_{max} by 18% and $AUC_{0\text{-}INF}$ by 61% and also decreased DP-5439 $AUC_{0\text{-}INF}$ by 57% with increased C_{max} by 37%; • Co-administration of efavirenz with a single dose of ripretinib was predicted to decrease ripretinib C_{max} by 24% and decrease $AUC_{0\text{-}INF}$ by 56% and also decrease DP-5439 $AUC_{0\text{-}INF}$ by 56% with decreased C_{max} by 7%	• Avoid concomitant use of QINLOCK with strong or moderate CYP3A inducers. • If a strong or moderate CYP3A inducer must be co-administered, increase QINLOCK dosing frequency from the recommended dose of 150 mg once daily to 150 mg twice daily during the co-administration period. If the concomitant strong or moderate CYP3A inducer is discontinued, resume QINLOCK dosage back to 150 mg once daily 14 days after the discontinuation of the CYP3A inducer. Monitor for clinical response and tolerability [see DOSAGE AND ADMINISTRATION].

CT=Clinical Trial; T=Theoretical

Studies of other CYP inhibition and induction:

In vitro studies with human hepatic microsomes suggest that both ripretinib and its active metabolite DP-5439 are likely to inhibit CYP2C8 at clinically relevant concentrations.

In vitro studies suggest that ripretinib is not an inducer of CYP1A2, CYP2B6, and CYP3A4 enzyme activity.

Studies with gastric pH altering medicines:

No clinically significant differences in the plasma exposure ($AUC_{0\text{-}INF}$ and C_{max}) to ripretinib and its active metabolite (DP-5439) were observed when a single dose of 50 mg ripretinib was co-administered with pantoprazole (a proton pump inhibitor) in healthy subjects.

Studies with drug transporters:

In vitro studies suggest ripretinib is an inhibitor of P-gp (P-glycoprotein) and BCRP (Breast Cancer Resistance Protein), and its active metabolite DP-5439 is an inhibitor of BCRP and MATE1 (Multidrug And Toxin Extrusion Protein 1). In addition, DP-5439 is a substrate for P-gp and BCRP.

9.5 Drug-Food Interactions

A high-fat, high-calorie meal administered to patients before a 150 mg dose of ripretinib increased the exposure of ripretinib and its active metabolite (DP-5439) when compared to dose administration under modified fasting conditions. The increase in exposure was not considered clinically relevant. QINLOCK may be taken with or without food [see ACTION AND CLINICAL PHARMACOLOGY].

Grapefruit juice has CYP3A inhibitory activity. Therefore, ingestion of grapefruit juice while on QINLOCK therapy may lead to decreased ripretinib metabolism and increased ripretinib plasma concentrations. Patients who ingest grapefruit juice while taking QINLOCK should be monitored more frequently for adverse reactions (see Drug-Drug Interactions).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

St. John's Wort is a potent CYP3A inducer. Co-administration with QINLOCK may lead to increased ripretinib metabolism and decreased ripretinib plasma concentrations; therefore, concomitant use should be avoided (see Drug-Drug Interactions).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ripretinib is a tyrosine kinase inhibitor that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and Platelet-Derived Growth Factor Receptor A (PDGFRA) kinase signaling. Ripretinib inhibits KIT and PDGFRA kinase activity, including wild type and multiple primary and secondary mutations. Ripretinib also inhibits other kinases *in vitro*, such as PDGFRB, TIE2, VEGFR2, and BRAF.

10.2 Pharmacodynamics

Cardiac Electrophysiology

In a multicenter, phase 1, open-label, uncontrolled study of QINLOCK administered to patients with advanced malignancies, no large mean increase from baseline in QTc interval (i.e., >20 ms) was detected following treatment with QINLOCK at the recommended dose of 150 mg once daily after a single dose on Cycle 1, Day 1 (N=18) or during steady-state treatment on Cycle 1, Day 15 (N=13).

10.3 Pharmacokinetics

The pharmacokinetics of QINLOCK and its active metabolite (DP-5439) were evaluated following single doses in healthy subjects and following multiple doses in patients with advanced malignancies.

Table 7: Summary of Ripretinib and DP-5439 Pharmacokinetic Parameters

	C_{max}[a]	T_{max}[a]	$t_{½}$ (h)[b]	AUC_{0-12h}[a]	CL/F[b]	V_{ss}/F[b]
Ripretinib	761 (31.8%) ng/mL	2 (1-8) hours	14.8 (30.3%) hours	5678 (32.1%) ng•h/mL	15.3 (45.2%) L/hr	307 (38.6%) L
DP-5439	804 (45.5%) ng/mL	6 (1-8) hours	17.8 (23.3%)	7138 (44.4%) ng•h/mL	17.5 (62.7%) L/hr	507 (50.5%) L

AUC_{0-12h} = area under the concentration versus time curve 12 hours after dosing at steady state; C_{max} = maximum plasma concentration; CL/F = apparent systemic clearance; $t_{1/2}$ = half-life; T_{max} = time of observed maximum plasma concentration after a single dose; V_{ss}/F = Steady-state apparent volume of distribution

a. Data presented are geometric means (CV%) for C_{max} and $AUC_{0-12h,}$ median (range) for T_{max} at steady state (Day 15) after once daily doses of 150 mg in patients with advanced malignancies (N=11).

b. Geometric mean values (CV%) for $t_{½}$, CL/F and Vss/F (N=13) were obtained after a single oral dose of ripretinib 150 mg in healthy subjects

Absorption: Ripretinib exposure (C_{max} and AUC_{0-24}) was dose proportional within the dose range of 20-150 mg but less than dose proportional at doses of 200 mg and 250 mg. The active metabolite DP-5439 exposure (C_{max} and AUC_{0-24}) was less than dose proportional within the dose range studied. Steady state was achieved by Day 15 after once daily doses of 150 mg, and ripretinib and DP-5439 accumulated with a geometric mean ratio of 1.66 (55.3% CV) and 5.29 (48.7% CV) respectively, based on AUC.

A high-fat, high-calorie meal (consisting of approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively) administered to patients (N=12) 30 minutes before a 150 mg dose of ripretinib increased AUC_{0-24h} and C_{max} by approximately 30% and 22%, respectively, when compared to dose administration under modified fasting conditions (no food consumption for at least 2 hours before and 1 hour after drug intake). The AUC_{0-24h} and C_{max} of the active metabolite of ripretinib, DP-5439, were also increased following drug administration with a high-fat meal. These changes were not considered clinically relevant.

Distribution: Ripretinib and DP-5439 were highly bound to plasma protein in humans (mean bound fraction was ≥ 99%). Ripretinib and DP-5439 bind to both human serum albumin and α-1 acid glycoprotein (98.6%). The geometric mean systemic volume of distribution is approximately 307 L (38.6% CV) for ripretinib and approximately 507 L (50.5% CV) for DP-5439.

Metabolism: The primary metabolic pathways for ripretinib appeared to be N-dealkylation and oxidation, although a definitive mass balance study has not been performed in humans. *In vitro* data suggested that CYP3A4/5 is the major metabolizer of ripretinib while CYP2C8 and CYP2D6 were implicated as only minor metabolizers. DP-5439 is the major phase I metabolite, exhibiting similar pharmacological activity, extent of protein binding, and steady-state concentrations compared to ripretinib. DP-5439 was metabolized primarily by CYP3A4 and to a lesser extent by CYP2D6, CYP2C8, CYP2C9 and CYP2C19.

Elimination: Geometric mean half-life ($t_{½}$) after a single dose of ripretinib 150 mg in healthy subjects was 14.8 hours (30.3% CV) for ripretinib and 17.8 hours (23.3% CV) for DP-5439. The geometric mean apparent clearance was15.3 L/hr (45.2% CV) for ripretinib and 17.5 L/hr (62.7% CV) for DP-5439. After a single oral dose of ripretinib 150 mg in healthy subjects, approximately 34% of the drug was eliminated in the feces as the parent compound and 6% as the metabolite DP-5439, and 0.02% of the drug was eliminated in urine as the parent compound and 0.1% as the metabolite DP-5439. A definitive mass balance study has not been performed in humans, but in preclinical species, C-labeled ripretinib dosed to Sprague-Dawley rats (oral) and beagle dogs (intravenous [iv]), resulted in greater than 89% of the radioactive dose being excreted in feces and 1.8% or less in the urine.

Special Populations and Conditions

Geriatrics: Based on a population pharmacokinetics analysis which included patients 19 to 87 years old (median age is 60 years), age does not have a clinically meaningful effect on the pharmacokinetics of ripretinib.

Sex: In a population pharmacokinetics analysis, female patients were estimated to have 29% lower apparent clearance (CL/F) for ripretinib resulting in a predicted 40% increase in steady state exposure (AUC) than male patients. This effect on exposure is not considered to be clinically relevant.

Ethnic origin: Based a population pharmacokinetics analysis which included 78% White, 7.71% Black, and 5.71% Asian patients, ethnic origin does not have a clinically meaningful effect on the pharmacokinetics of ripretinib.

Hepatic Insufficiency: The effect of varying degrees of hepatic impairment as defined by Child-Pugh classification on the pharmacokinetics of ripretinib and DP-5439 was studied in a clinical trial (Study DCC-2618-01-004).

In participants with mild hepatic impairment, there were no clinically significant changes in ripretinib and DP-5439 $AUC_{0\text{-last}}$ and C_{max} when compared to matched healthy subjects.

In participants with moderate hepatic impairment, ripretinib $AUC_{0\text{-tlast}}$ was 2-fold higher while C_{max} was unchanged compared to matched healthy participants. The combined $AUC_{0\text{-tlast}}$ of ripretinib and DP-5439 was approximately 1.5-fold higher.

In participants with severe hepatic impairment, ripretinib $AUC_{0\text{-tlast}}$ was 2.6-fold higher, C_{max} was 0.8-fold lower, and the combined $AUC_{0\text{-tlast}}$ of ripretinib and DP-5439 was 1.4-fold higher, compared to matched healthy participants.

The observed magnitude of increase in ripretinib and combined ripretinib and DP-5439 exposures in subjects with hepatic impairment (Child-Pugh A, B and C) is unlikely to be clinically relevant based on the known safety profile of ripretinib.No dose adjustment is recommended in patients with mild (Child-Pugh A), moderate (Child-Pugh B), or severe hepatic impairment (Child-Pugh C) [see DOSAGE AND ADMINISTRATION].

Renal Insufficiency: Mild and moderate renal impairment do not have a clinically meaningful effect on the pharmacokinetics of ripretinib based on a population pharmacokinetics analysis which included patients with mild (CrCl 60 to 89 mL/min estimated by Cockcroft-Gault, N=93) and moderate (CrCl 30 to 59 mL/min, N=45) renal impairment. The pharmacokinetics and safety of ripretinib in patients with severe renal impairment (CrCl 15 to 29 mL/min) have not been studied [see DOSAGE AND ADMINISTRATION].

Obesity: Based on a population pharmacokinetic analysis which included patients with body weight 39 to 138 kg (median weight is 74.4 kg), body weight does not have a clinically meaningful effect on the pharmacokinetics of ripretinib.

11 STORAGE, STABILITY AND DISPOSAL

Store in the original container at room temperature (15°C to 25°C).

Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

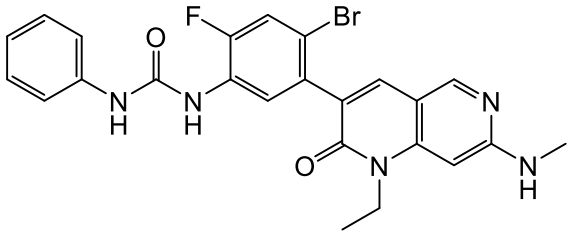
Drug Substance

Proper/Common name: Ripretinib

Chemical name: 1-(4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl)-3-phenylurea

Molecular formula and molecular mass: $C_{24}H_{21}BrFN_5O_2$ / 510.36 g/mol

Structural formula:



Physicochemical properties: Ripretinib is a white to off-white crystalline solid. Ripretinib is a lipophilic, weak base compound, practically insoluble in aqueous media.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Locally advanced or metastatic gastrointestinal stromal tumor (GIST) who had been previously treated with prior anticancer therapies

Table 8: Summary of study design and patient demographics for the pivotal study in patients with gastrointestinal stromal tumor (GIST)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
DCC-2618-03-001 (INVICTUS)	Randomized (2:1), double-blind, placebo-controlled trial	150 mg QINLOCK, oral, until disease progression or unacceptable toxicity	129	60.1 years (29 to 83 years)	Male / female

The efficacy and safety of QINLOCK were evaluated in an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial (INVICTUS) in patients with unresectable, locally advanced or metastatic gastrointestinal stromal tumor (GIST) who had been previously treated with prior anticancer therapies including treatment with imatinib mesylate, sunitinib malate, and regorafenib. Randomization was stratified by number of prior

anticancer treatments (3 versus ≥4) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 or 2).

The primary efficacy outcome measure was progression-free survival (PFS) based on disease assessment by blinded independent central review (BICR) using modified RECIST 1.1 criteria, in which lymph nodes and bone lesions were not target lesions and a progressively growing new tumor nodule within a pre-existing tumor mass must meet specific criteria to be considered unequivocal evidence of progression. The secondary efficacy outcome measures included objective response rate (ORR) by BICR and overall survival (OS).

Participants were randomized to receive 150 mg QINLOCK (N=85) or placebo (N=44) orally once daily administered in continuous 28-day cycles. Treatment continued until disease progression or unacceptable toxicity. Individual participant blinding was broken at the time of disease progression as assessed by BICR review and all patients on placebo arm were offered to cross-over to QINLOCK.

The demographic characteristics were median age of 60 years (29 to 83 years) with 61.2% aged 18-64 years; male (56.6 %); White (75.2%); and ECOG performance status of 0 (41.9%), 1 (49.6%), or 2 (8.5%). The median number of prior therapies was 3 and 62% had received 3 prior therapies. Of the 129 patients, 25.6% had received 4 prior therapies, 7.8% has received 5 prior therapies, 0.8% had received 6 prior therapies, and 3.9% had received 7 prior therapies.

A statistically significant improvement in PFS was demonstrated among patients treated with QINLOCK compared to placebo (see Table 9 and Figure 1).

The hierarchical statistical testing order was PFS followed by ORR and then OS. No formal testing of OS was conducted since the formal comparison of ORR was not statistically significant (see Table 9). The OS results for the placebo arm include the survival time of patients taking placebo who, following BICR progression, crossed over to QINLOCK treatment. At the time of final analysis, 29 (65.9%) patients had crossed over from the placebo arm and received at least one dose of QINLOCK.

Study Results

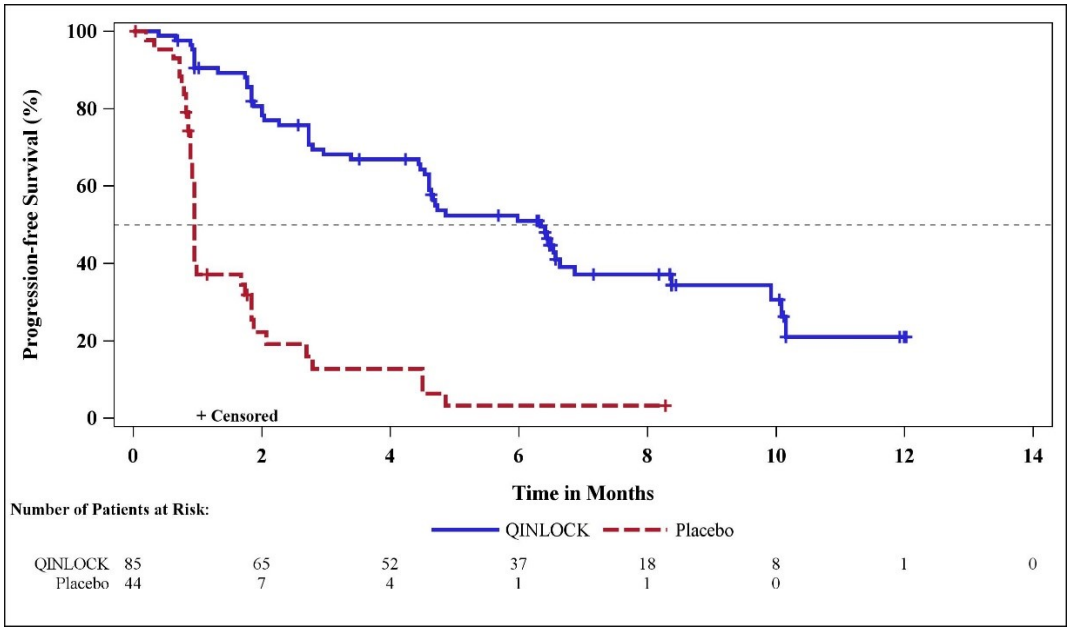
Efficacy results from INVICTUS are summarized in Table 9.

Table 9: Efficacy Results of INVICTUS

	QINLOCK (N=85)	**Placebo (N=44)**
Progression-Free Survival (PFS)[a]		
Number of patients with PFS event, N (%)	51 (60.0)	37 (84.1)
Median PFS (months) (95% CI)	6.3 (4.6, 6.9)	1.0 (0.9, 1.7)
p-value[b]	<0.0001	
HR (95% CI)[c]	0.15 (0.09, 0.25)	
Objective Response Rate (ORR)[a]		
Objective Response Rate (%) (95% CI)	9.4 (4.2, 17.7)	0 (0, 8.0)
p-value[d]	0.0504	
Overall Survival (OS)		
Number of Deaths, N (%)	26 (30.6)	26 (59.1)
Median OS (months) (95% CI)	15.1 (12.3, 15.1)	6.6 (4.1, 11.6)
HR (95% CI)[c]	0.36 (0.21, 0.62)	

	QINLOCK (N=85)	Placebo (N=44)
BICR=Blinded Independent Central Review; HR=Hazard Ratio; CI=Confidence Interval a. Assessed per BICR. b. p-value is based on 2-sided stratified Log Rank test. c. Hazard ratio is based on Cox proportional hazards regression model. This model includes treatment and randomization stratification factors as fixed factors. d. p-value is based on Fisher's exact test.		

Figure 1: Kaplan-Meier Curve of Progression-Free Survival (Months)



15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Ripretinib was tested by oral gavage in repeat-dose studies of up to 13 weeks in rats (30, 100, or 300 mg/kg/day) and dogs (2.5, 5, or 10 mg/kg/day). Toxicities observed included missing/discoloration of the growing incisor teeth in rats, and discolored skin, skin lesions, alopecia/thinning hair coat in rats and dogs. During the recovery phase, reversal was noted for the scaly skin, thinning hair coat, and sores and scabs. Other ripretinib-related clinical observations included decreased body weight and body weight gain, and decreased food consumption. At 300 mg/kg/day dose marked degeneration of Brunner's glands of the proximal duodenum was observed in female rats. Ripretinib related increased osteoblastic surface and/or decreased trabeculae of the femur occurred in rats administered ≥30 mg/kg/day. Minimal to moderate hypertrophy/hyperplasia of blood vessels occurred in the liver, lungs, and/or mesenteric lymph node of rats administered ≥100 mg/kg/day. Minimally to moderately

increased lymphoid follicles occurred in the white pulp of the spleen in rats administered ≥30 mg/kg/day. Clinical pathology changes observed in the dosing phase in rats and dogs were generally dose-dependent in magnitude, did not progress over time, and were suggestive of red blood cell loss, an inflammatory and/or a stress response, and liver alteration. Most findings exhibited evidence of reversibility at the end of the recovery phase although there was evidence of persistence of the inflammatory response into the recovery phase. The no observed adverse effect level (NOAEL) for ripretinib after 13 weeks of dosing was 100 mg/kg/day in rats and 5 mg/kg/day in dogs, corresponding to AUC_{0-24} values of 20,800 ng•hr/mL and 1910 ng•hr/mL in rats and dogs, respectively.

Carcinogenicity

Carcinogenicity studies have not been conducted with ripretinib.

Genotoxicity

Ripretinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and in an *in vivo* rat bone marrow micronucleus assay.

Reproductive and Developmental Toxicology

Ripretinib is teratogenic in rats. In an embryo-fetal development study in which female Sprague-Dawley pregnant rats were administered daily doses of ripretinib during organogenesis, ripretinib was given to pregnant rats once daily from gestational days 6 through 18 at doses 1, 5, or 20 mg/kg/day. Dose-related malformations primarily associated with the cardiovascular and skeletal systems were observed at a dose of 20 mg/kg/day (approximately one half of the human exposure at 150 mg once daily). Visceral malformations were confined to the great vessels and included interrupted or retroesophageal aortic arch and retroesophageal subclavian artery. Skeletal malformations occurred in the skull bones, ribs, vertebrae, and paws including fusion of the exoccipital bone to the first cervical vertebra, branched and fused ribs; anomalies of the cervical, thoracic, caudal, and sacral vertebrae; absent forepaw phalanges, and absent metacarpals.

An increased incidence of anatomic variations, indicative of developmental toxicity, also occurred at 20 mg/kg/day. Visceral variations involved the great vessels and included malpositioned carotid and subclavian artery origins, malpositioned subclavian artery, and absent or elongated innominate artery. Skeletal variations involved the ribs, vertebrae, and sternebrae and included misshapen and nodulated ribs; bipartite, incompletely ossified, or unossified vertebral centra; and small or misshapen vertebral arches. Reductions in ossified forelimb and hindlimb phalanges, hindlimb metatarsals, and caudal vertebrae were also observed at 20 mg/kg/day. Additional indications of developmental toxicity at this dose included anatomic variations and reduced fetal body weight.

Ripretinib was given orally to pregnant Crl: KBL(NZW) rabbits once daily from gestational days 7 through 19 at doses of 0, 2, 10, 40, and 150 mg/kg/day. Ripretinib-related abortions and maternal body weight loss were noted at 150 mg/kg/day. Administration of ripretinib resulted in increased post-implantation loss and reduced fetal body weights at 40 mg/kg/day.

Dedicated fertility studies in male animals were not conducted with ripretinib. In repeat dose toxicity studies ripretinib related bilateral degeneration/atrophy of the testis and increased cellular debris of the epididymis with corresponding decreased testis and epididymis weights were observed in male rats at the 30 and 300 mg/kg/day doses. Decreased testis and epididymis weights were not reversed by the end of the recovery period.

Special Toxicology Studies

In vitro phototoxicity assessment in 3T3 mouse fibroblast cells suggest that ripretinib exhibits a potential for phototoxicity at clinically relevant concentrations following exposure to UVA and UVB radiation.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]QINLOCK™ Ripretinib Tablets

Read this carefully before you start taking **QINLOCK** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **QINLOCK.**

Serious Warnings and Precautions

QINLOCK can cause:
- Serious heart problems like heart failure
- High blood pressure
- Serious skin problems:
    - New skin cancers (squamous cell carcinoma or melanoma).

The symptoms are listed in the 'Serious side effects and what to do about them' table. It is found later in this leaflet.

What is QINLOCK used for?
QINLOCK is used to treat adults with gastrointestinal stromal tumor (GIST), which is a type of soft tissue cancer (sarcoma). The cancer must have been treated before with other cancer drugs for GIST including imatinib, sunitinib, and regorafenib.

How does QINLOCK work?
QINLOCK helps slow down the growth of cancer cells in your body.

What are the ingredients in QINLOCK?
Medicinal ingredients: ripretinib
Non-medicinal ingredients: crospovidone, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and silicon dioxide.

QINLOCK comes in the following dosage forms:
Tablets, 50 mg

Do not use QINLOCK if:
- You are allergic to any ingredients in this drug or the bottle.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take QINLOCK. Talk about any health conditions or problems you may have, including if you:
- have or ever had heart problems, like:
    - heart failure and decreased blood flow to your heart.

- have or had high blood pressure.
- have or had skin problems:
  - Avoid strong sunlight, sunlamps, and other sources of ultraviolet (UV) light, such as tanning beds. Your skin may be more sensitive to sunlight while taking QINLOCK and for at least 1 week after stopping treatment with QINLOCK.
  - Use a sunscreen and wear protective clothing that covers your skin when you are exposed to strong sunlight.
  - Skin problems include:
    - New skin cancers (squamous cell carcinoma (SCC) or melanoma).
    - Palmar-plantar erythrodysesthesia syndrome (PPES).
  - Tell your healthcare professional if you have new skin problems or if they change or worsen.
- had or plan to have surgery. Wounds may not heal well during treatment with QINLOCK. If you plan on having the following surgeries:
  - Minor surgery: Your treatment should stop at least three days before and after the surgery.
  - Major surgery: Your treatment should stop at least five days before and after the surgery.
- are younger than 18 years of age.
- have or had an allergic reaction to a drug similar to QINLOCK.

Other warnings you should know about:

Pregnancy and Breastfeeding:
Female Patients
- Avoid becoming pregnant while taking QINLOCK. QINLOCK can harm your unborn baby.
- If you can get pregnant, your healthcare professional will do a pregnancy test before starting treatment.
- You should not take QINLOCK if you are pregnant or if you are still able to get pregnant and are not using highly effective birth control.
- If you can get pregnant, use highly effective birth control methods:
  - for two weeks before your first dose of QINLOCK, while taking QINLOCK, and for at least one menstrual cycle after your final dose.
  - It is not known if QINLOCK can affect your birth control steroid. Use a barrier method of contraception, like condoms, if you are using birth control steroids.
- Tell your healthcare professional right away if you become pregnant or think you are pregnant during treatment with QINLOCK. Your healthcare professional will explain the risks to you.
- It is not known if QINLOCK passes into breast milk. Do not breastfeed during treatment with QINLOCK and for at least two weeks after the final dose. Talk to your healthcare professional about the best way to feed your baby during this time.

Male Patients
- If your partner can get pregnant, use highly effective birth control methods:
  - for two weeks before your first dose of QINLOCK, while taking QINLOCK, and for at least one of your partner's menstrual cycles after your final dose.
- QINLOCK can harm your fertility. This may affect the ability to have children. Talk to your healthcare professional about ways to maintain your fertility before you start treatment.

Check-Ups and Testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They may check:

- that your heart is working properly.
- your blood pressure.
- your skin health.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

For example, the following may interact with QINLOCK:

- Clarithromycin, used to treat infections
- Indinavir, ritonavir, cobicistat and efavirenz, used to treat HIV infection
- Ketoconazole and itraconazole, used to treat fungal infections
- Rifampicin, used to treat bacterial infections, primarily tuberculosis
- Phenytoin and carbamazepine, used to treat seizures and epilepsy
- St John's Wort, used to treat depression
- Grapefruit juice

How to take QINLOCK:

- Take QINLOCK exactly as your healthcare professional tells you. Check with your healthcare professional if you are not sure.
- Take at the same time each day.
- Take with or without food.
- Swallow tablets whole. Do not chew, split or crush tablets. Do not take tablets if they are broken, cracked or damaged.
- Tell your healthcare professional about any side effects you may have when taking QINLOCK.

Recommended Adult Dose:

- Take 150 mg (three 50 mg tablets) of QINLOCK once daily by mouth, at the same time each day.
- Your healthcare professional will monitor your health. They may interrupt, reduce, stop, or increase your dose. This may occur based on your current health, if you take certain other medications or if you have certain side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much **QINLOCK**, contact your healthcare professional, hospital emergency department or regional poison control center immediately, even if there are no symptoms.

Missed Dose:

If you are taking QINLOCK twice a day and a dose is missed or not taken at the usual time:

- If you are less than 4 hours late, take the missed dose as soon as you remember. Take the next dose at your regular time.
- If you are more than 4 hours late, skip the dose for that day. Wait until the regular time for your next dose.
- If you vomit after taking a dose, do not take an additional dose and continue with the next scheduled dose.

If you are taking QINLOCK once a day and your dose is missed or not taken at the usual time:
- If you are less than 8 hours late, take the missed dose as soon as you remember. Take the next dose at your regular time.
- If you are more than 8 hours late, skip the dose for that day. Wait until the regular time for your next dose.
- If you vomit after taking a dose, do not take another dose on that day. Take your next dose on the next day at the usual time.

What are possible side effects from using QINLOCK?
These are not all the possible side effects you may feel when taking QINLOCK. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Hair thinning or hair loss
- Tiredness or weakness
- Nausea
- Constipation
- Abdominal, back or joint pain
- Muscle spasms or pain (myalgia)
- Diarrhea
- Decreased appetite
- Decreased weight
- Heartburn
- Mouth sores
- Vomiting
- Headache
- Fever
- Dry or itchy skin
- Dizziness
- Swelling

QINLOCK can cause abnormal blood test results. Your healthcare professional will do some tests before, during and after your treatment. More frequent tests might be needed. They will tell you if your test results are abnormal and if you need treatment.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling		√ (even if you have no symptoms)	√ (if severe)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
in your ankles and legs, racing pulse or heart palpitations			
Palmar-plantar erythrodysesthesia syndrome (PPES): thickening skin, blisters, redness, swelling, and pain on the palms of hands and/or the soles of the feet, tingling or burning, tightness of the skin		√	
COMMON			
Heart failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			√
Myocardial ischemia (lack of blood flow to the heart which can lead to heart attack): sudden chest pain, pressure or discomfort, feeling faint, feeling anxious, shortness of breath, irregular heartbeat, nausea, sudden heavy sweating			√
Squamous cell carcinoma, melanoma (skin cancers and disorders)**:** Rash, new or changing skin lesion, thickening of skin, rough scaly patches of skin, open sores, new or changing skin colour.		√	
RARE			
Hypersensitivity (allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, watery eyes			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store QINLOCK in the original container at room temperature (15ºC to 25ºC).

Keep out of reach and sight of children.

If you want more information about QINLOCK:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) or by calling the Importer and Distributor Medison Pharma Canada Inc. at 1-800-696-1341

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