

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use QINLOCK safely and effectively. See full prescribing information for QINLOCK.

QINLOCK® (ripretinib) tablets, for oral use
Initial U.S. Approval: 2020

RECENT MAJOR CHANGES

Warnings and Precautions, Photosensitivity (5.6) 09/2022

INDICATIONS AND USAGE

QINLOCK is a kinase inhibitor indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib. (1)

DOSAGE AND ADMINISTRATION

Recommended Dosage: 150 mg orally once daily with or without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Palmar-Plantar Erythrodysesthesia Syndrome:** Based on severity, withhold QINLOCK and resume at same or reduced dose. (2.2, 5.1)
- **New Primary Cutaneous Malignancies:** Perform dermatologic evaluations when initiating QINLOCK and routinely during treatment. (5.2)
- **Hypertension:** Do not initiate QINLOCK in patients with uncontrolled hypertension and monitor blood pressure during treatment. Based on severity, withhold QINLOCK and then resume at same or reduced dose or permanently discontinue. (2.2, 5.3)
- **Cardiac Dysfunction:** Assess ejection fraction by echocardiogram or MUGA scan prior to initiating QINLOCK and during treatment, as clinically indicated. Permanently discontinue QINLOCK for Grade 3 or 4 left ventricular systolic dysfunction. (2.2, 5.4)

- **Risk of Impaired Wound Healing:** Withhold QINLOCK for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of QINLOCK after resolution of wound healing complications has not been established. (5.5)
- **Photosensitivity:** May cause photosensitivity reactions. Advise patients to limit direct ultraviolet exposure. (5.6)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 20\%$) were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia, and vomiting. The most common Grade 3 or 4 laboratory abnormalities ($\geq 4\%$) were increased lipase and decreased phosphate. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Deciphera Pharmaceuticals, LLC, at 1-888-724-3274 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Strong CYP3A Inhibitors:** Monitor more frequently for adverse reactions. (7.1)
- **Strong CYP3A Inducers:** Avoid concomitant use of strong CYP3A inducers. (7.1)
- **Moderate CYP3A Inducers:** Avoid concomitant use of moderate CYP3A inducers. If a moderate CYP inducer cannot be avoided, increase ripretinib dose frequency to twice daily. (2.3, 7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

QINLOCK is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of QINLOCK is 150 mg orally once daily with or without food until disease progression or unacceptable toxicity.

Instruct patients to swallow tablets whole.

Advise patients to take QINLOCK at the same time each day.

Advise patients to take a missed dose if less than 8 hours have passed since the missed scheduled dose.

Advise patients not to take an additional dose if vomiting occurs after taking QINLOCK and to continue with their next scheduled dose.

2.2 Dosage Modifications for Adverse Reactions

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 Dosage Modifications for QINLOCK for Adverse Reactions

| Adverse Reaction | Severity ^a | QINLOCK Dosage Modifications |
|--|-----------------------|---|
| Palmar-Plantar Erythrodysesthesia Syndrome (PPES) [see Warnings and Precautions (5.1)] | Grade 2 | <ul style="list-style-type: none"> • Withhold QINLOCK until Grade \leq1 or baseline. If recovered within 7 days, resume QINLOCK at same dose; otherwise resume at reduced dose. • Consider re-escalating QINLOCK if maintained at Grade \leq1 or baseline for at least 28 days. • If PPES recurs, withhold QINLOCK until Grade \leq1 or baseline and then resume QINLOCK at a reduced dose regardless of time to improvement. |
| | Grade 3 | <ul style="list-style-type: none"> • Withhold QINLOCK for at least 7 days or until Grade \leq1 or baseline (maximum 28 days). Resume QINLOCK at a reduced dose. • Consider re-escalating QINLOCK if maintained at Grade \leq1 or baseline for at least 28 days. |
| Hypertension [see Warnings and Precautions (5.3)] | Grade 3 | <ul style="list-style-type: none"> • If symptomatic, withhold QINLOCK until symptoms have resolved and blood pressure is controlled. • If blood pressure is controlled to Grade \leq1 or baseline, resume QINLOCK at the same dose; otherwise, resume QINLOCK at reduced dose. • If Grade 3 hypertension recurs, withhold QINLOCK until symptoms have resolved and blood pressure is controlled. Resume QINLOCK at a reduced dose. |
| | Grade 4 | Permanently discontinue QINLOCK. |
| Left Ventricular Systolic Dysfunction [see Warnings and Precautions (5.4)] | Grade 3 or 4 | Permanently discontinue QINLOCK. |

| Adverse Reaction | Severity ^a | QINLOCK Dosage Modifications |
|---|-----------------------|---|
| Arthralgia or Myalgia [see Adverse Reactions (6.1)] | Grade 2 | <ul style="list-style-type: none"> Withhold QINLOCK until Grade ≤ 1 or baseline. If recovered within 7 days, resume QINLOCK at same dose; otherwise resume QINLOCK at reduced dose. Consider re-escalating QINLOCK if maintained at Grade ≤ 1 or baseline for at least 28 days. If arthralgia or myalgia recurs, withhold QINLOCK until Grade ≤ 1 or baseline and then resume QINLOCK at a reduced dose regardless of time to improvement. |
| | Grade 3 | <ul style="list-style-type: none"> Withhold QINLOCK for at least 7 days or until Grade ≤ 1 or baseline (maximum of 28 days). Resume QINLOCK at a reduced dose. Consider re-escalating QINLOCK if maintained at Grade ≤ 1 or baseline for at least 28 days. |
| Other Adverse Reactions [see Adverse Reactions (6.1)] | Grade 3 or 4 | <ul style="list-style-type: none"> Withhold QINLOCK until Grade ≤ 1 or baseline (maximum 28 days), and then resume QINLOCK at a reduced dose; otherwise permanently discontinue. Consider re-escalating QINLOCK if no recurrence of the adverse reaction for at least 28 days. If Grade 3 or 4 recurs, permanently discontinue QINLOCK. |

^a Graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

2.3 Dose Modifications for Moderate CYP3A Inducers

Avoid concomitant use of moderate CYP3A inducers during QINLOCK treatment.

If a moderate CYP3A inducer cannot be avoided, 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 moderate CYP3A inducer is discontinued, resume QINLOCK dosage back to 150 mg once daily 14 days after the discontinuation of the moderate CYP3A inducer. [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg, white to off-white, oval shaped, debossed with “DC1” on one side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Palmar-Plantar Erythrodysesthesia Syndrome

In INVICTUS, Grade 1-2 palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 21% of the 85 patients who received QINLOCK [see Adverse Reactions (6.1)]. 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.

Based on severity, withhold QINLOCK and then resume at same or reduced dose [see Dosage and Administration (2.2)].

5.2 New Primary Cutaneous Malignancies

In INVICTUS, cutaneous squamous cell carcinoma (cuSCC) occurred in 4.7% of the 85 patients who received QINLOCK, with a median time to event of 4.6 months (range: 3.8 to 6 months). In the pooled safety population, cuSCC and keratoacanthoma occurred in 7% and 1.9% of patients, respectively.

In INVICTUS, melanoma occurred in 2.4% of the 85 of patients who received QINLOCK. In the pooled safety population, melanoma occurred in 0.9% of patients.

Perform dermatologic evaluations when initiating QINLOCK and routinely during treatment. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Continue QINLOCK at the same dose.

5.3 Hypertension

In INVICTUS, Grade 1-3 hypertension occurred in 14% of the 85 patients who received QINLOCK, including Grade 3 hypertension in 7% [see *Adverse Reactions (6.1)*].

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. Based on severity, withhold QINLOCK and then resume at same or reduced dose or permanently discontinue [see *Dosage and Administration (2.2)*].

5.4 Cardiac Dysfunction

In INVICTUS, cardiac failure occurred in 1.2% of the 85 patients who received QINLOCK. In the pooled safety population, cardiac dysfunction (including cardiac failure, acute left ventricular failure, diastolic dysfunction, and ventricular hypertrophy) occurred in 1.7% of patients, including Grade 3 adverse reactions in 1.1%.

In INVICTUS, 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. In the pooled safety population, 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.

In INVICTUS, cardiac dysfunction led to dose discontinuation in 1.2% of the 85 patients who received QINLOCK. The safety of QINLOCK has not been assessed in patients with a baseline ejection fraction below 50%.

Assess ejection fraction by echocardiogram or MUGA scan prior to initiating QINLOCK and during treatment, as clinically indicated. Permanently discontinue QINLOCK for Grade 3 or 4 left ventricular systolic dysfunction [see *Dosage and Administration (2.2)*].

5.5 Risk of Impaired 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.

Withhold QINLOCK for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of QINLOCK after resolution of wound healing complications has not been established.

5.6 Photosensitivity

QINLOCK may cause photosensitivity reactions. In all patients treated with QINLOCK in clinical trials (n=621), photosensitivity reactions occurred in 0.6% of patients.

Advise patients to limit direct ultraviolet exposure during treatment with QINLOCK and for at least one week after discontinuation of treatment.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, QINLOCK can cause fetal harm when administered to a pregnant woman. Oral administration of ripretinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations primarily associated with the cardiovascular and skeletal systems, anatomic variations, decreased fetal body weight, and increased post-implantation loss at exposures approximately one half of the recommended dose of 150 mg once daily based on area under the curve (AUC).

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with QINLOCK and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with QINLOCK and for 1 week after the last dose [see *Use in Specific Populations (8.1, 8.3)*, *Nonclinical Toxicology (13.1)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Palmar-Plantar Erythrodysesthesia Syndrome [see *Warnings and Precautions (5.1)*]
- New Primary Cutaneous Malignancies [see *Warnings and Precautions (5.2)*]
- Hypertension [see *Warnings and Precautions (5.3)*]
- Cardiac Dysfunction [see *Warnings and Precautions (5.4)*]
- Photosensitivity [see *Warnings and Precautions (5.6)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Unless otherwise specified, the pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to QINLOCK as a single agent in 351 patients with advanced solid tumors enrolled in either an open-label dose finding with cohort expansion trial or INVICTUS. Among the patients who received QINLOCK in these trials, 52% were exposed for 6 months or longer and 21% were exposed for greater than one year.

Gastrointestinal Stromal Tumor

Patients Who Received Prior Treatment with Imatinib, Sunitinib and Regorafenib

The safety of QINLOCK was evaluated in INVICTUS [see *Clinical Studies (14)*]. Patients received QINLOCK 150 mg taken orally once daily (n=85) or placebo (n=43). Among the patients who received QINLOCK, 46% were exposed for 6 months or longer and 3.5% were exposed for greater than one year.

Serious adverse reactions 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%), and vomiting (2.4%).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received QINLOCK. Adverse reactions 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%).

Dosage interruptions due to an adverse reaction occurred in 24% of patients who received QINLOCK. Adverse reactions 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 reaction occurred in 7% of patients who received QINLOCK. Adverse reactions 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.

The most common adverse reactions (≥20%), were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, PPES, and vomiting. The most common Grade 3 or 4 laboratory abnormalities (≥4%) were increased lipase and decreased phosphate.

Table 2 summarizes the adverse reactions in INVICTUS.

Table 2: Adverse Reactions (≥10%) in Patients with Gastrointestinal Stromal Tumor Who Received QINLOCK in INVICTUS

| Adverse Reaction | QINLOCK (N=85) | | Placebo (N=43) | |
|--|-------------------|------------|-------------------|------------|
| | Grades 1-4 | Grades 3-4 | Grades 1-4 | Grades 3-4 |
| Skin and subcutaneous tissue | | | | |
| 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 |
| General | | | | |
| Fatigue | 42 | 3.5 | 23 | 2.3 |
| Peripheral edema | 17 | 1.2 | 7 | 0 |
| Asthenia | 13 | 1.2 | 14 | 4.7 |
| Gastrointestinal | | | | |
| Nausea | 39 | 3.5 | 12 | 0 |
| Abdominal pain | 36 | 7 | 30 | 4.7 |
| Constipation | 34 | 1.2 | 19 | 0 |
| Diarrhea | 28 | 1.2 | 14 | 2.3 |
| Vomiting | 21 | 3.5 | 7 | 0 |
| Stomatitis | 11 | 0 | 0 | 0 |
| Musculoskeletal and connective tissue | | | | |
| Myalgia | 32 | 1.2 | 12 | 0 |
| Arthralgia | 18 | 0 | 4.7 | 0 |
| Muscle spasms | 15 | 0 | 4.7 | 0 |
| Metabolism and nutrition | | | | |
| Decreased appetite | 27 | 1.2 | 21 | 2.3 |
| Investigations | | | | |
| Decreased weight | 19 | 0 | 12 | 0 |
| Nervous system | | | | |
| Headache | 19 | 0 | 4.7 | 0 |
| Vascular | | | | |
| Hypertension | 14 | 7 | 4.7 | 0 |
| Respiratory, thoracic and mediastinal | | | | |
| Dyspnea | 13 | 0 | 0 | 0 |

Table 3 summarizes the laboratory abnormalities in INVICTUS.

Table 3: Select 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 | | | | |
| Increased activated partial thromboplastin time | 35 | 0 | 9 | 0 |
| Increased INR | 21 | 3.8 | 15 | 0 |
| Decreased neutrophil count | 10 | 0 | 2.5 | 0 |
| Chemistry | | | | |
| Increased lipase | 32 | 7 | 13 | 8 |
| Decreased phosphate | 26 | 4.9 | 2.5 | 0 |
| Increased triglycerides | 26 | 2.4 | 23 | 0 |
| Decreased calcium | 23 | 0 | 8 | 0 |
| Increased blood bilirubin | 22 | 0 | 5 | 2.5 |
| Increased CPK | 21 | 1.2 | 10 | 0 |
| Decreased sodium | 17 | 2.4 | 10 | 2.5 |
| Increased creatinine | 16 | 0 | 18 | 0 |
| Increased serum amylase | 13 | 1.2 | 5 | 0 |
| Increased ALT | 12 | 1.2 | 5 | 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. | | | | |

Other Adverse Reactions

Clinically relevant adverse reactions that occurred in <10% of patients in the pooled safety population included cardiac ischemic events (1.1%) (including acute coronary syndrome and fatal cardiac arrest or myocardial infarction). Photosensitivity occurred in 0.6% [see *Warnings and Precautions* (5.6)].

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on QINLOCK

Table 4 includes drug interactions that affect the pharmacokinetics of ripretinib.

Table 4: Drug Interactions that Affect QINLOCK

| <u>Strong CYP3A Inhibitors</u> | |
|---|--|
| <i>Clinical Impact</i> | <ul style="list-style-type: none"> • Coadministration of QINLOCK with a strong CYP3A inhibitor increased the exposure of ripretinib and its active metabolite (DP-5439), which may increase the risk of adverse reactions [see <i>Clinical Pharmacology (12.3)</i>]. |
| <i>Prevention or Management</i> | <ul style="list-style-type: none"> • Monitor patients more frequently for adverse reactions. |
| <u>Strong and Moderate CYP3A Inducers</u> | |
| <i>Clinical Impact</i> | <ul style="list-style-type: none"> • Coadministration of QINLOCK with a strong CYP3A inducer decreased the exposure of ripretinib and its active metabolite (DP-5439), which may decrease QINLOCK anti-tumor activity [see <i>Clinical Pharmacology (12.3)</i>]. • Coadministration of QINLOCK with moderate CYP3A inducers is predicted to decrease the exposure of ripretinib and its active metabolite (DP-5439), which may decrease QINLOCK anti-tumor activity [see <i>Clinical Pharmacology (12.3)</i>]. |
| <i>Prevention or Management</i> | <ul style="list-style-type: none"> • Avoid concomitant use of QINLOCK with strong CYP3A inducers. • Avoid concomitant use of QINLOCK with moderate CYP3A inducers. If a moderate CYP3A inducer cannot be avoided, increase 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 [see <i>Dosage and Administration (2.3)</i>]. |

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology (12.1)*], QINLOCK can cause fetal harm when administered to a pregnant woman. There are no available data on the use of QINLOCK in pregnant women to inform a drug-associated risk. Administration of ripretinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations primarily associated with the cardiovascular and skeletal systems, anatomic variations, reduced fetal body weight, and increased post-implantation loss at maternal exposures that were approximately equal to the human exposure at the recommended dose of 150 mg (see *Data*). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study investigating daily doses of ripretinib administered during the period of organogenesis in rats, ripretinib resulted in malformations primarily associated with the cardiovascular and skeletal systems, including interrupted or retroesophageal aortic arch and retroesophageal subclavian artery,

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 at a dose of 20 mg/kg/day (approximately one half of the human exposure at the recommended dose of 150 mg). An increased incidence of anatomic variations were also observed at 20 mg/kg/day. Variations included malpositioned carotid and subclavian artery origins, malpositioned subclavian artery, absent or elongated innominate artery, misshapen and nodulated ribs, bipartite, incompletely ossified, or unossified vertebral centra, small or misshapen vertebral arches, and reductions in ossified forelimb and hindlimb phalanges, hindlimb metatarsals, and caudal vertebrae.

In a preliminary embryo-fetal development study investigating the administration of ripretinib in rabbits during the period of organogenesis, ripretinib resulted in total loss of pregnancy at doses of 150 mg/kg (approximately 3.5 times the human exposure at the recommended dose of 150 mg). At a dose of 40 mg/kg (approximately 2.1 times the human exposure at the recommended dose of 150 mg), toxicities included increased post-implantation loss and decreased fetal body weights.

8.2 Lactation

Risk Summary

There are no data regarding the presence of ripretinib or its metabolites in either human milk or its effects on a breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with QINLOCK and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

QINLOCK can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to the initiation of QINLOCK [*see Use in Specific Populations (8.1)*].

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 1 week after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose.

Infertility

Based on findings from animal studies, QINLOCK may impair fertility in males of reproductive potential [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of QINLOCK in pediatric patients have not been established.

Animal Toxicity Data

In 13-week repeat-dose studies in rats there were dose-dependent findings of increased osteoblastic surface and decreased trabeculae of the femur at doses ≥ 30 mg/kg/day (approximately one half of the human exposure at the recommended dose of 150 mg). There were additional findings of missing or discolored teeth that were accompanied by dose-dependent incisor degeneration at doses ≥ 30 mg/kg/day.

8.5 Geriatric Use

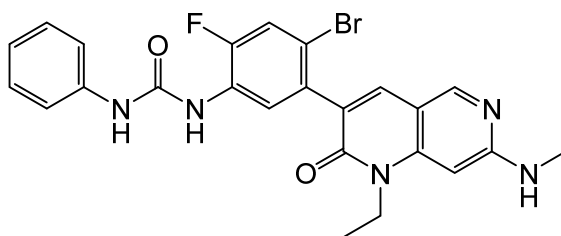
Of the 85 patients in INVICTUS who received QINLOCK 150 mg orally once daily, 24% were between 65 to 74 years of age and 9% were 75 years of age or older. Clinical studies of QINLOCK did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dose adjustment is recommended in patients with hepatic impairment (Child-Pugh A, B, or C) [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Ripretinib is a kinase inhibitor. The chemical name of ripretinib is 1-(4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl)-3-phenylurea. The molecular formula is $C_{24}H_{21}BrFN_5O_2$ and the molecular weight is 510.36 g/mol. The chemical structure of ripretinib is shown below:



Ripretinib is a white to off-white crystalline solid. Ripretinib is a lipophilic, weak base, and practically insoluble in aqueous media.

QINLOCK is available as a white to off-white, oval tablets for oral use containing 50 mg of ripretinib. The tablet is debossed with “DC1” on one side. Each tablet contains the following inactive ingredients: crospovidone, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 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, including wild type, primary, and secondary mutations. Ripretinib also inhibits other kinases in vitro, such as PDGFRB, TIE2, VEGFR2, and BRAF.

12.2 Pharmacodynamics

Exposure-Response Relationships

Ripretinib exposure-response relationships and the time course of pharmacodynamics have not been fully characterized.

Cardiac Electrophysiology

No large mean increase in QTc interval (i.e. >20 ms) was detected following treatment with QINLOCK at the recommended dose of 150 mg taken orally once daily.

12.3 Pharmacokinetics

The pharmacokinetics of ripretinib and its equally active metabolite (DP-5439) were characterized in clinical studies. In patients with advanced malignancies, ripretinib AUC_{0-24h} increased proportionally over a dose range of 20-250 mg (0.13 to 1.67 times the recommended dose), but C_{max} was less than dose proportional; DP-5439

C_{max} and AUC_{0-24h} were less than dose proportional within the dose range of 50-250 mg (0.33 to 1.67 times the recommended dose).

No clinically significant differences in the C_{max} and AUC_{0-24h} were observed between administration of QINLOCK with a high-fat meal (150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively) and under fasted conditions. The pharmacokinetic parameters of ripretinib and DP-5439 are summarized in Table 5.

Table 5: Pharmacokinetic Parameters of Ripretinib and DP-5439

| Parameter | | Ripretinib | DP-5439 |
|--|-------------------------------|-------------------|---------------------------|
| <u>General Information</u> | | | |
| Steady state exposure following QINLOCK 150 mg once daily [Mean (CV%)] | C_{max} (ng/mL) | 761 (32) | 804 (46) |
| | AUC_{0-12h} (ng•h/mL) | 5678 (32) | 7138 (44) |
| Time to steady state [Days] | | 14 | 14 |
| Accumulation ratio (AUC_{0-12h}) [Mean (CV%)] ^a | | 1.7 (55) | 5.29 (49) |
| <u>Absorption</u> | | | |
| T_{max} [Median in hours] ^b | | 4 | 15.6 |
| <u>Distribution</u> | | | |
| Plasma protein binding (in vitro) | Human serum albumin | 99.8% | 99.7% |
| | α -1 acid glycoprotein | 99.4% | >99.8% |
| Steady state apparent volume of distribution, L [Mean (CV%)] ^b | | 307 (39) | 507 (51) |
| <u>Elimination</u> | | | |
| Apparent clearance, L/hr [Mean (CV%)] ^b | | 15.3 (45) | 17.5 (63) |
| Half-life, hours [Mean (CV%)] ^b | | 14.8 (30) | 17.8 (23) |
| <u>Metabolism</u> | | | |
| Metabolic pathways | Major | CYP3A4 | CYP3A4 |
| | Minor | CYP2C8 and CYP2D6 | CYP2C8, CYP2E1 and CYP2D6 |
| <u>Excretion</u> | | | |
| Excretion pathways | Feces | 34% | 6% |
| | Urine | 0.02% | 0.1% |
| ^a . Estimated based on cycle 1, day 15 ^b . After a single oral dose of 150 mg CV=coefficient of variation; C_{max} =maximum plasma concentration; AUC_{0-12h} =area under the plasma concentration-time curve from time zero to 12 hours; AUC_{0-24h} =area under the plasma concentration-time curve from time zero to 24 hours; T_{max} =time to maximum concentration | | | |

Specific Populations

No clinically significant differences in the pharmacokinetics of ripretinib were observed based on age (19 to 87 years), sex, race (White, Black, and Asian), body weight (39 to 138 kg), tumor (GIST or other solid tumors), prior gastrectomy, mild to moderate renal impairment (CL_{cr} 30 to <90 mL/min estimated by Cockcroft-Gault), and mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin 1 to 1.5 × ULN and AST any).

The effects of severe renal impairment (CL_{cr} 15 to 29 mL/min) on the pharmacokinetics of ripretinib have not been studied.

Patients with Hepatic Impairment

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

In subjects with moderate hepatic impairment, ripretinib AUC_{0-last} increased 2-fold while C_{max} was unchanged when compared to matched healthy subjects. The combined AUC_{0-last} of ripretinib and DP-5439 increased 1.5-fold.

In subjects with severe hepatic impairment, ripretinib AUC_{0-last} increased 2.6-fold and C_{max} decreased by 24% when compared to matched healthy subjects. The combined AUC_{0-last} of ripretinib and DP-5439 increased by 1.4-fold.

The observed magnitude of increase in ripretinib and the combination of ripretinib and DP-5439 exposures in subjects with hepatic impairment is unlikely to be clinically relevant based on the known safety profile of ripretinib.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A Inhibitors: Coadministration of QINLOCK with itraconazole (a strong CYP3A inhibitor and also a P-gp inhibitor) increased ripretinib C_{max} by 36% and AUC_{0-inf} by 99% and also increased DP-5439 AUC_{0-inf} by 99% with no change in its C_{max}.

Strong CYP3A Inducers: Coadministration of QINLOCK with rifampin (a strong CYP3A inducer) decreased ripretinib C_{max} by 18% and AUC_{0-inf} by 61% and also decreased DP-5439 AUC_{0-inf} by 57% with increased C_{max} by 37%.

Moderate CYP3A Inducers: Coadministration of QINLOCK with efavirenz (a moderate CYP3A inducer) was predicted to decrease ripretinib C_{max} by 24% and decrease AUC_{0-inf} by 56%.

Proton Pump Inhibitors: No clinically significant differences in the plasma exposure to ripretinib and DP-5439 were observed when QINLOCK was coadministered with pantoprazole (a proton pump inhibitor).

In Vitro Studies

CYP Enzymes: Ripretinib and DP-5439 are inhibitors of CYP2C8. Ripretinib and DP-5439 are not inducers of CYP1A2, CYP2B6, or CYP3A4.

Transporter Systems: Ripretinib is an inhibitor of P-gp (P-glycoprotein) and BCRP (Breast Cancer Resistance Protein). DP-5439 is a substrate for P-gp and BCRP. DP-5439 is an inhibitor of BCRP and MATE1 (Multidrug And Toxin Extrusion Protein 1).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ripretinib.

Ripretinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay or clastogenic in either an in vitro human lymphocyte culture micronucleus assay or an in vivo rat bone marrow micronucleus assay.

Dedicated fertility studies in male animals were not conducted with ripretinib. Findings in male reproductive organs occurred in repeat-dose toxicity studies and included degeneration of the testes and cellular debris of the epididymis in males administered ≥ 30 mg/kg/day (approximately one half of the human exposure at the recommended dose of 150 mg).

14 CLINICAL STUDIES

The efficacy of QINLOCK was evaluated in INVICTUS, an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial (NCT03353753). Eligible patients had unresectable, locally advanced or metastatic gastrointestinal stromal tumor (GIST) and had received prior treatment with imatinib, sunitinib, and regorafenib. Randomization was stratified by prior lines of therapy (3 versus ≥ 4) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 or 2). Patients received QINLOCK 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. Tumor response assessments were performed every 28 days through for the first 4 months and then every 56 days thereafter. The major 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. Additional efficacy outcome measures included objective response rate (ORR) by BICR and overall survival (OS). Patients randomized to receive placebo could be treated with QINLOCK at the time of disease progression.

A total of 129 patients were randomized, 85 to QINLOCK and 44 to placebo.

Patient characteristics of the intent-to-treat (ITT) population in INVICTUS were median age of 60 years (range: 29 to 83 years), with 39% aged ≥ 65 years; 57% were male; 75% were White; and 92% had an ECOG performance status of 0 or 1. Sixty-three percent (63%) of patients received 3 prior therapies and 37% received 4 or more prior therapies. Sixty-six percent (66%) of patients randomized to placebo switched to QINLOCK after disease progression.

Efficacy results from INVICTUS are summarized in [Table 6](#).

Table 6: Efficacy Results of INVICTUS

| | QINLOCK (N=85) | Placebo (N=44) |
|--|-------------------|-------------------|
| Progression-Free Survival^a | | |
| Number of events (%) | 51 (60) | 37 (84) |
| Progressive disease | 46 (54) | 32 (73) |
| Deaths | 5 (6) | 5 (11) |
| Median PFS (months) (95% CI) | 6.3 (4.6, 6.9) | 1.0 (0.9, 1.7) |
| Hazard ratio (95% CI) ^c | 0.15 (0.09, 0.25) | |
| p-value ^b | < 0.0001 | |
| Overall Response Rate^a | | |
| Overall Response Rate (%) | 9 | 0 |
| (95% CI) | (4.2, 18) | (0, 8) |
| p-value ^d | 0.0504 | |
| Overall Survival^c | | |
| Number of deaths (%) | 26 (31) | 26 (59) |
| Median OS (months) (95% CI) | 15.1 (12.3, 15.1) | 6.6 (4.1, 11.6) |

| | |
|------------------------------------|-------------------|
| Hazard ratio (95% CI) ^c | 0.36 (0.21, 0.62) |
|------------------------------------|-------------------|

BICR=Blinded Independent Central Review; 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 regression model. This model includes treatment and randomization stratification factors as fixed factors.
- d. Based on Fisher's exact test. The p-value is not statistically significant.
- e. Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints of ORR and OS.

Figure 1: Kaplan-Meier Curve of Progression-Free Survival in INVICTUS

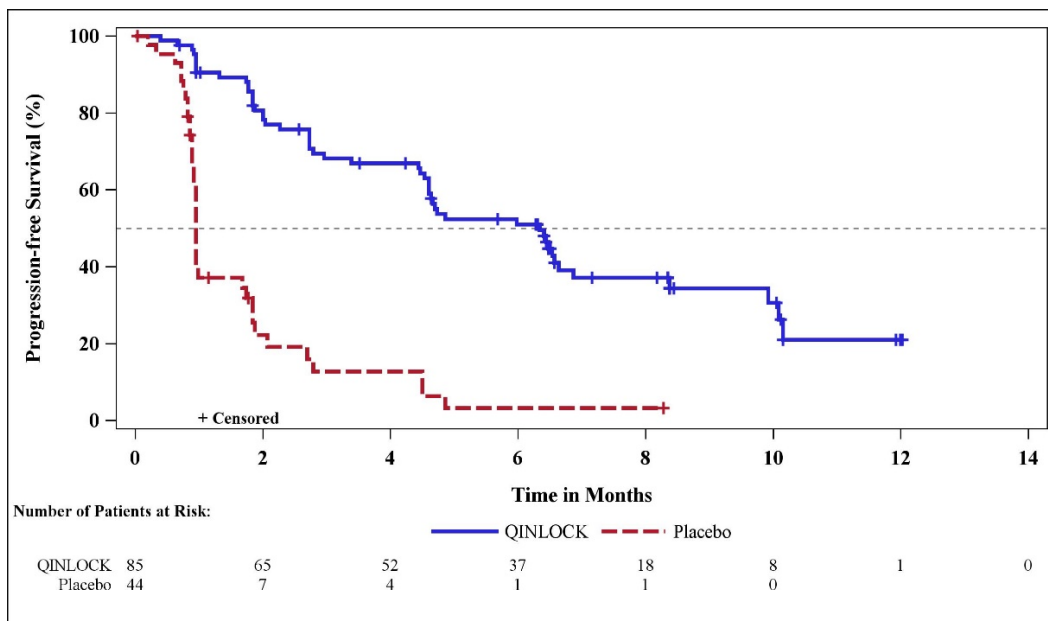
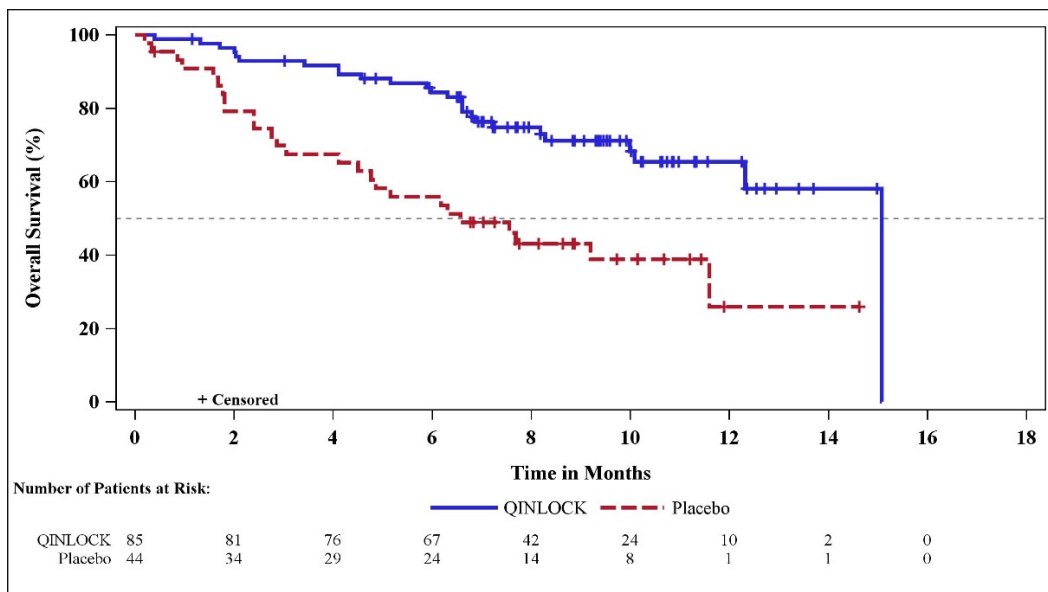


Figure 2: Kaplan-Meier Curve of Overall Survival in INVICTUS



16 HOW SUPPLIED/STORAGE AND HANDLING

QINLOCK 50 mg tablets are white to off-white, oval shaped, and debossed with “DC1” on one side.

90-count bottles NDC 73207-101-30

Dispense to patient in original container only. Store in the original container with the desiccant to protect from moisture and light. Replace cap securely each time after opening. Do not discard desiccant.

Store at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Palmar-Plantar Erythrodysesthesia Syndrome

Advise patients to contact their healthcare provider immediately if they experience severe skin changes [*see Warnings and Precautions (5.1)*].

New Primary Cutaneous Malignancies

Advise patients to contact their healthcare provider immediately for change in or development of new skin lesions [*see Warnings and Precautions (5.2)*].

Hypertension

Advise patients that hypertension may develop during treatment with QINLOCK and that blood pressure should be monitored regularly during treatment [*see Warnings and Precautions (5.3)*].

Cardiac Dysfunction

Advise patients that cardiac failure may develop during treatment with QINLOCK and that signs or symptoms of cardiac failure should be regularly monitored during treatment. Advise patients to contact their healthcare provider immediately for signs or symptoms of cardiac dysfunction [*see Warnings and Precautions (5.4)*].

Risk of Impaired Wound Healing

Advise patients that QINLOCK may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure [*see Warnings and Precautions (5.5)*].

Photosensitivity

Inform patients that there is a potential risk of photosensitivity reactions with QINLOCK. Advise patients to limit direct ultraviolet exposure by using sunscreen or protective clothing during treatment with QINLOCK [*see Warnings and Precautions (5.6)*].

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.7), Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective contraception during treatment with QINLOCK and for 1 week after the last dose [*see Use in Specific Populations (8.3)*].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with QINLOCK and for 1 week after the last dose [*see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

Lactation

Advise females not to breastfeed during treatment with QINLOCK and for 1 week after the last dose [*see Use in Specific Populations (8.2)*].

Infertility

Advise males of reproductive potential that QINLOCK may impair fertility [*see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [*see Drug Interactions (7.1)*].

Dosage and Administration

Instruct patients to take QINLOCK at the same time each day (once daily) with or without food. Advise patients to swallow tablets whole. Inform patients about what to do in the event they miss a dose or vomit after taking a dose of QINLOCK [*see Dosage and Administration (2.1)*].

Storage Instructions

Store QINLOCK in the original container at room temperature between 20°C to 25°C (68°F to 77°F).

Manufactured for and marketed by:

Deciphera Pharmaceuticals, LLC
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