Date: 05 November 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Qinlock

International non-proprietary name: ripretinib
Pharmaceutical form: tablets
Dosage strength: 50 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Deciphera Pharmaceuticals
Marketing Authorisation No.: 68199
Decision and Decision date: approved on 07 October 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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Table of contents

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance ripretinibum of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 or 2 of the TPA. The Orphan Status was granted on 5 November 2020.

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Treatment of adult patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

2.2.2 Approved Indication

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 (see section «Clinical efficacy»).

2.2.3 Requested Dosage

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

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	27 November 2020
Formal control completed	21 December 2020
Predecision	13 April 2021
Answers to Predecision	4 July 2021
Final Decision	07 October 2021
Decision	approval

Swissmedic has not assessed the primary data of this application and is taking over the results of the assessment of the foreign reference authority FDA. The current SwissPAR refers to the publicly available Assessment Report Qinlock, dated 24 July 2019 issued by FDA.

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3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is taking over the results of the assessment of the foreign reference authority FDA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report Qinlock, dated 24 July 2019 issued by FDA.

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4 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority FDA. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report Qinlock, dated 24 July 2019 issued by FDA.

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5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority FDA. The current SwissPAR relating to clinical aspects refers to the publicly available Assessment Report Qinlock, dated 24 July 2019 issued by FDA.

5.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Qinlock was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approFved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

QINLOCK

Composition

Active substances

Ripretinib

Excipients

Crospovidone, hypromellose acetate succinate, lactose monohydrate (179 mg per tablet), magnesium stearate, microcrystalline cellulose, and silicium dioxid.

Pharmaceutical form and active substance quantity per unit

Tablets for oral use.
1 tablet contains 50 mg of ripretinib.

Appearance
White to off-white oval tablet, debossed with 'DC1' on one side of the tablet.

Indications/Uses

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 (see section «Clinical efficacy»).

Dosage/Administration

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.

Dose adjustment following undesirable effects/interactions

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»]*	Grade 2	• Withhold QINLOCK until Grade ≤1 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 ≤1 or baseline for at least 28 days. • If PPES recurs, withhold QINLOCK until Grade ≤1 or baseline and then resume QINLOCK at a reduced dose regardless of time to improvement.
	Grade 3	• Withhold QINLOCK for at least 7 days or until Grade ≤1 or baseline (maximum 28 days). Resume QINLOCK at a reduced dose. • Consider re-escalating QINLOCK if maintained at Grade ≤1 or baseline for at least 28 days.
Hypertension *[see «Warnings and Precautions»]*	Grade 3	• If symptomatic, withhold QINLOCK until symptoms have resolved and blood pressure is controlled. • If blood pressure is controlled to Grade ≤1 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»]*	Grade 3 or 4	Permanently discontinue QINLOCK.
Arthralgia or Myalgia *[see «Undesirable Effects»]*	Grade 2	• 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.

Adverse Reaction	Severity[a]	QINLOCK Dosage Modifications
	Grade 3	• 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 «Undesirable Effects»]*	Grade 3 or 4	• 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).

Patients with hepatic disorders

No dose adjustment is recommended in patients with mild hepatic impairment. QINLOCK has not been studied in patients with moderate or severe hepatic impairment or severe renal impairment (see «Properties and Effects»).

Patients with renal disorders

No dose adjustment is recommended in patients with mild to moderate renal impairment. QINLOCK has not been studied in patients with moderate or severe hepatic impairment or severe renal impairment. A recommended dosage of QINLOCK has not been established for patients with severe renal impairment (see «Properties and Effects»).

Elderly patients

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.

Children and adolescents

The safety and effectiveness of QINLOCK in pediatric patients have not been established. There is no data available.

Contraindications

None.

Warnings and precautions

Palmar-Plantar Erythrodysesthesia Syndrome
Palmar-plantar erythrodysaesthesia syndrome (PPES) occurred in patients treated with QINLOCK (see «Undesirable effects»).

Based on severity, withhold QINLOCK and then resume at same or reduced dose (see «Dosage/Administration»).

Hypertension
Hypertension was observed with QINLOCK (see «Undesirable effects»). 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/Administration»).

Cardiac Failure
Cardiac failure was observed with QINLOCK. Ejection fraction should be assessed by echocardiogram or MUGA scan prior to initiating QINLOCK and during treatment, as clinically indicated. QINLOCK should be permanently discontinued for Grade 3 or 4 left ventricular systolic dysfunction. The safety of QINLOCK has not been assessed in patients with a baseline left ventricular ejection fraction below 50% (see «Undesirable effects»).

New primary cutaneous tumours
Cutaneous squamous cell carcinoma (CuSCC) and melanomas were reported in patients receiving QINLOCK. Dermatologic evaluations should be performed when initiating QINLOCK and routinely during treatment. Suspicious skin lesions should be managed with excision and dermatopathologic evaluation (see «Undesirable effects»). Continue QINLOCK at the same dose.

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.

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 (see «Preclinical data»).

Other ingredients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interactions

Effect of other drugs on QINLOCK

Table 2: Drug interactions that affect QINLOCK

Strong CYP3A inhibitors	
Clinical impact	• Co-administration 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 “Properties and Effects”).
Prevention or management	• Monitor patients more frequently for adverse reactions.
Strong CYP3A inducers	
Clinical impact	• Co-administration of QINLOCK with a strong CYP3A inducer may decrease the exposure of ripretinib and its active metabolite (DP-5439), which may decrease QINLOCK anti-tumour activity (see “Properties and Effects”).
Prevention or management	• Avoid concomitant use of QINLOCK with strong CYP3A inducers.

Clinical Studies

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 $AUC_{0\text{-}INF}$ by 99% and also increased its active metabolite (DP-5439) $AUC_{0\text{-}INF}$ by 99% with no change in its C_{max}. Strong CYP3A and P-gp inhibitors are to be used with caution and patients should be monitored.

Strong CYP3A Inducers: The effect of coadministration of QINLOCK with a strong CYP3A inducer has not been studied. Ripretinib and DP-5439 are metabolized by CYP3A.

Gastric Acid Reducing Agents: 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).

Pregnancy, lactation

Pregnancy

No data are available on the use of QINLOCK in pregnant women that would allow an estimate of the risk associated with the product. Animal studies have shown reproductive toxicity (see “Preclinical data”). Based on findings from animal studies and its mechanism of action (see «Properties/Effects»), QINLOCK can cause fetal harm when administered to a pregnant woman. (see «Preclinical data»). QINLOCK should not be used during pregnancy unless clearly necessary.

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

Lactation

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 at least 1 week after the final dose.

Infertility

Based on findings from animal studies, QINLOCK may impair fertility in males of reproductive potential (see «Preclinical data»).

Effects on ability to drive and use machines

No studies on the effects of QINLOCK on the ability to drive or use machines have been performed. It is not known whether QINLOCK alters the ability to drive or use machines.

Undesirable effects

Summary of the safety profile

The frequencies of adverse reactions were assessed from a pooled dataset of two clinical studies in which 392 adults were treated with QINLOCK for advanced malignancies, including 299 patients with GIST. The median duration of treatment among 85 patients in the double-blind period of the INVICTUS study was 23.86 weeks (1.3–121.9).

Serious adverse drug reactions occurring with a frequency ≥1% in patients treated with QINLOCK were anaemia (3.8%), dyspnoea (2.3%), vomiting (2.0%), nausea (1.8%), fatigue (1.5%), blood bilirubin increased (1.3%), constipation (1.0%), and muscular weakness (1.0%).

The most frequently observed adverse drug reactions (≥10%) in patients treated with QINLOCK were fatigue (51.0%), alopecia (50.8%), nausea (39.8%), myalgia (37.8%), constipation (37.2%), diarrhoea (32.7%), weight decreased (26.5%), vomiting (25.8%), lipase increased (23.7%), muscle spasms (23.7%), arthralgia (21.2%), headache (20.7%), dyspnoea (20.2%), dry skin (17.6%), back pain (15.6%), cough (15.6%), blood bilirubin increased (14.0%), peripheral oedema (13.8%), hypophosphataemia (12.2%), pain in extremity (12.0%), pruritus (11.0%) and seborrhoeic keratosis (11.0%).

Grade 3/4 adverse drug reactions occurring with a frequency ≥2% in patients treated with QINLOCK were lipase increased (14.8%), anaemia (14.0%), abdominal pain (8.2%), hypertension (6.9%), fatigue (4.1%), hypophosphataemia (4.1%), vomiting (2.6%), dyspnoea (2.0%), diarrhoea (2.0%) and blood bilirubin increased (2.0%).

List of adverse reactions

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Very common: Seborrhoeic keratosis (11.0%).
Common: Squamous cell carcinoma of skin, Fibrous histiocytoma, Melanocytic naevus, Skin papilloma.
Uncommon: Melanoma

Endocrine disorders
Common: Hypothyroidism.

Metabolism and nutrition disorders
Very common: Hypophosphataemia (12.2%).

Psychiatric disorders
Common: Depression.

Nervous system disorders
Very common: Headache (20.7%).
Common: Peripheral sensory neuropathy.

Cardiac disorders
Common: Cardiac failure, Tachycardia.

Vascular disorders
Very common: Hypertension (19.4%)

Respiratory, thoracic and mediastinal disorders
Very common: Dyspnoea (20.2%), Cough (15.6%).

Gastrointestinal disorders
Very common: Nausea (39.8%), Constipation (37.2%), Diarrhoea (32.7%), Vomiting (25.8%).
Common: Stomatitis, Abdominal pain upper.

Skin and subcutaneous tissue disorders
Very common: Alopecia (50.8%), Palmar-plantar erythrodysesthesia syndrome (29.8%), Dry skin (17.6%), Pruritus (11.0%).
Common: Hyperkeratosis, Rash maculopapular, Pruritus generalised, Dermatitis acneiform.

Musculoskeletal and connective tissue disorders
Very common: Myalgia (37.8%), Muscle spasms (23.7%), Arthralgia (21.2%), Back pain (15.6%), Pain in extremity (12.0%).
Common: Muscular weakness, Musculoskeletal chest pain

General disorders and administration site conditions
Very common: Fatigue (51.0%), Oedema peripheral (13.8%).

Investigations
Very common: Weight decreased (26.5%), Lipase increased (23.7%), Blood bilirubin increased (14.0%)

Common: Alanine aminotransferase increased

Description of selected adverse drug reactions as defined above

Palmar-plantar erythrodysesthesia syndrome (PPES)
In a placebo-controlled study, palmar-plantar erythrodysesthesia syndrome (PPES) was reported in 19 of 85 (22.4%) patients in the QINLOCK arm and no patients in the placebo arm. PPES led to dose discontinuation in 2.4% of patients, dose interruption in 3.5% of patients, and dose reduction in 1.2% of patients. All events were mild or moderate in severity (58% Grade 1 and 42% Grade 2) .

In the pooled safety population, PPES occurred in 29.8% of 392 patients, including Grade 3 adverse reactions in 0.5%. The median time to onset and duration of the first event was 8.1 weeks (range: 0.3 weeks to 112.1 weeks) and 24.3 weeks (range: 0.9 to 191.7 weeks), respectively.

Hypertension
In a placebo-controlled study, the incidence of hypertension in patients treated with Qinlock was 15.3% vs. 4.7% of patients who received placebo.
In the pooled safety population, hypertension occurred in 19.4% of 392 patients, including Grade 3 adverse reactions in 6.9%.

Cardiac failure
In a placebo-controlled study, cardiac failure occurred in 1.2% of 85 patients who received QINLOCK all of whom discontinued treatment. No patient experienced cardiac failure in the placebo group.
In the pooled safety population, cardiac failure (including cardiac failure, cardiac failure acute, acute left ventricular failure, and diastolic dysfunction) occurred in 1.5% of 392 patients, including Grade 3 adverse reactions in 1.0%.

In the pooled safety population, 299 of 392 patients had a baseline and at least one post-baseline echocardiogram. Grade 3 decreased ejection fraction occurred in 4.0% of the 299 patients.

Cutaneous Malignancies
In a placebo-controlled study, cutaneous squamous cell carcinoma (cuSCC; Keratoacanthoma, Squamous cell carcinoma of skin, Squamous cell carcinoma; Squamous cell carcinoma of head and neck; all events regardless of causality) was reported in 5.9% of the 85 patients receiving QINLOCK. CuSCC was not reported in placebo-treated patients.
In the pooled safety population, cuSCC occurred in 8.7% of 392 patients including Grade 3 adverse reactions in 0.5%. Melanoma (all events regardless of causality) occurred in 0.3% of 392 patients.

Myalgia and Arthralgia
In the double-blind period of the INVICTUS study, myalgia was observed in 36.5% of QINLOCK treated patients versus 11.6% of placebo treated patients. Arthralgia was observed in 20.0% of QINLOCK treated patients versus 4.7% of placebo treated patients.

In the pooled safety population, myalgia was observed in 37.8% of 392 patients including Grade 3 adverse reactions in 0.5%. Arthralgia was observed in 21.2% of 392 patients.
Alopecia
In a placebo-controlled study, alopecia was reported in 44 of 85 (51.8%) patients in the QINLOCK arm and 2 (4.7%) patients in the placebo arm. Alopecia led to dose interruption in 1.2% of patients and dose reduction in 1.2% of patients. No patients discontinued treatment due to alopecia.
In the pooled safety population, 199 of 392 (50.8%) patients receiving ripretinib developed alopecia. The median time to onset of the first event was 8.3 weeks (range: 0.1 weeks to 89.1 weeks); the median duration of the events was 25.0 weeks (range: 1.1 to 181.1 weeks).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no known specific antidote for QINLOCK overdose. In the event of suspected overdose, QINLOCK should be discontinued immediately, and best supportive care initiated by a medical professional, and the patient should be observed until clinical stabilization.

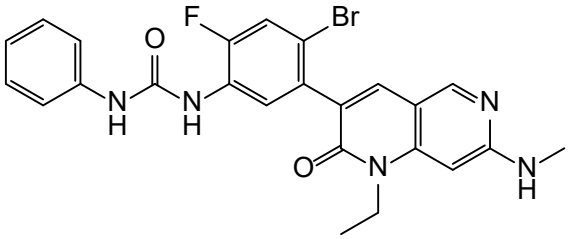
Properties/Effects

ATC code

L01EX19

Mechanism of action

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.

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.

Pharmacodynamics

Exposure-Response Relationships

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

Cardiac electrophysiology

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

Clinical efficacy

The efficacy of QINLOCK was evaluated in INVICTUS, an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial (NCT03353753). Enrolled patients had unresectable, locally advanced or metastatic gastrointestinal stromal tumor (GIST) Included patients had progression or intolerance to 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.

Patients in the QINLOCK arm had a median PFS of 6.3 months (95% CI: 4.6, 6.9) compared to 1.0 month (95% CI: 0.9, 1.7) in the placebo arm, which significantly reduced the risk of disease progression or death by 85% (hazard ratio of 0.15, p<0.0001).

ORR was observed in 8 patients in the ripretinib arm (9.4%) compared with 0% for placebo (p=0.0504). QINLOCK demonstrated a median OS of 15.1 months (95% CI: 12.3, 15.1) compared to 6.6 months (95% CI: 4.1, 11.6) in the placebo arm (hazard ratio of 0.36, 95% CI: 0.21, 0.62).

Pharmacokinetics

The pharmacokinetics of ripretinib and its equally active metabolite (DP-5439) were evaluated following single doses in healthy subjects and multiple doses in patients with advanced malignancies; the results are summarized in Table 3.

Table 3: Pharmacokinetic Parameters of Ripretinib and DP-5439

Parameter		**Ripretinib**	**DP-5439**
General Information			
Steady state exposure following QINLOCK 150 mg once daily [Mean (CV%)]	C_{max} (ng/mL)	761 (32)	804 (46)
	$AUC_{0\text{-}12h}$ (ng•h/mL)	5678 (32)	7138 (44)

Dose proportionality following single doses of QINLOCK in patients with advanced malignancies:		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.	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).
Time to steady state [Days]		14	14
Accumulation ratio (AUC_{0-12h}) [Mean (CV%)][a]		1.7 (55)	5.29 (49)
Absorption			
T_{max} [Median in hours][b]		4	15.6
Effect of Food		No clinically significant differences in the C_{max} and AUC_{0-24h} were observed between administration of QINLOCK with a high-fat meal[c] and under fasted conditions.	
Distribution			
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)
Elimination			
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)
Metabolism			
Metabolic pathways	Major	CYP3A4	CYP3A4
	Minor	CYP2C8 and CYP2D6	CYP2C8, CYP2E1 and CYP2D6
Excretion[b]			
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

c. A high fat meal consisted of approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively

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

Kinetics in specific patient groups

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 (CLcr 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 any AST). The effects of severe renal impairment (CLcr 15 to 29 mL/min) or moderate to severe hepatic impairment (total bilirubin >1.5 × ULN, any AST) on the pharmacokinetics of ripretinib have not been studied.

Preclinical data

Repeat dose toxicity

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.

Mutagenicity

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.

Carcinogenicity

Carcinogenicity studies have not been conducted with ripretinib.

Reproductive toxicity

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.

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).

Fertility

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).

Other information

Incompatibilities
Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Store at room temperature (15-25°C) in the original packaging. 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.

Keep out of the reach of children.

Authorisation number

68199 (Swissmedic)

Packs

Pack size with 90 tablets. [A]

Marketing authorisation holder

Deciphera Pharmaceuticals (Schweiz) AG, Zug

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