ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

QINLOCK 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of ripretinib.

Excipient with known effect

Each tablet contains 179 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to off-white, approximately 9 × 17 mm, oval shaped tablet, debossed with ‘DC1' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

QINLOCK should be prescribed by physicians experienced in the administration of anticancer agents.

Posology

The recommended dose is 150 mg ripretinib (three 50 mg tablets) taken once daily at the same time each day with or without food.

If the patient misses a dose of QINLOCK within 8 hours of the time it is usually taken, the patient should be instructed to take it as soon as possible and then take the next dose at the regularly scheduled time. If a patient misses a dose by more than 8 hours of the time it is usually taken, the patient should be instructed not to take the missed dose and simply resume the usual dosing schedule on the following day.

In case of vomiting after QINLOCK administration, the patient should not take a replacement dose and should resume the dosing schedule the next day at the usual time.

Treatment with QINLOCK should continue as long as benefit is observed or until unacceptable toxicity (see section 4.4).

Posology adjustments
Dose interruptions or dose reductions may be required based on individual safety and tolerability. The recommended dose reduction for adverse reactions is 100 mg orally, once daily.

QINLOCK should be permanently discontinued in patients who are unable to tolerate 100 mg orally once daily. The recommended dose modifications for QINLOCK for adverse reactions are provided in Table 1.

Table 1: Recommended dose modifications for adverse reactions

Adverse reaction	**Severity[a]**	**QINLOCK dose modifications**
Palmar-Plantar Erythrodysaesthesia Syndrome (PPES) (see sections 4.4 and 4.8)	Grade 2	• Withhold until Grade ≤1 or baseline. If recovered within 7 days, resume at same dose; otherwise resume at reduced dose. • Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days. • If PPES recurs, withhold until Grade ≤1 or baseline and then resume at a reduced dose regardless of time to improvement.
	Grade 3	• Withhold for at least 7 days or until Grade ≤1 or baseline (maximum 28 days). Resume at a reduced dose. • Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days.
Hypertension (see sections 4.4 and 4.8)	Grade 3	• If symptomatic, withhold until symptoms have resolved and blood pressure is controlled. • If blood pressure is controlled to Grade ≤1 or baseline, resume at the same dose; otherwise, resume at reduced dose. • If Grade 3 hypertension recurs, withhold until symptoms have resolved and blood pressure is controlled. Resume at a reduced dose.
	Grade 4	Permanently discontinue.
Left ventricular systolic dysfunction (see sections 4.4 and 4.8)	Grade 3 or 4	Permanently discontinue.
Arthralgia or myalgia (see section 4.8)	Grade 2	• Withhold until Grade ≤1 or baseline. If recovered within 7 days, resume at same dose; otherwise resume at reduced dose. • Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days. • If arthralgia or myalgia recurs, withhold until Grade ≤1 or baseline and then resume at a reduced dose regardless of time to improvement.
	Grade 3	• Withhold for at least 7 days or until Grade ≤1 or baseline (maximum of 28 days). Resume at a reduced dose. • Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days.
Other adverse reactions (see section 4.8)	Grade 3 or 4	• Withhold until Grade ≤1 or baseline (maximum 28 days), and then resume at a reduced dose; otherwise permanently discontinue. • Consider re-escalating if no recurrence of the adverse reaction for at least 28 days. • If Grade 3 or 4 recurs, permanently discontinue.

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

Concomitant medicinal products

Concomitant medicinal products that are strong or moderate inducers of CYP3A should be avoided (see sections 4.4 and 4.5). If a strong or moderate CYP3A inducer must be co-administered, the QINLOCK dosing frequency may be increased during the co-administration period. For strong inducers, the dose may be increased from 150 mg once daily to 150 mg twice daily. For patients taking QINLOCK twice daily, if the patient misses a dose within 4 hours of the time it is usually taken, the

patient should be instructed 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, the patient should be instructed not to take the missed dose and simply resume the usual dosing schedule. Close monitoring of overall efficacy and safety is recommended in these patients.

Special populations

Renal impairment
No dose adjustment is recommended in patients with mild and moderate renal impairment (see section 5.2). Only limited clinical data are available in patients with severe renal impairment [creatinine clearance (CLcr) <30 mL/min]. A recommended dose of QINLOCK has not been established in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is recommended in patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C). Data in patients with severe hepatic impairment is limited, thus close monitoring of overall safety is recommended in these patients.

Elderly
In clinical studies, no clinically relevant differences were observed between elderly (aged >65 years) and younger patients (aged ≤ 65 and ≥ 18 years) (see section 5.1).

Paediatric population
The safety and efficacy of QINLOCK in children below 18 years of age have not been established (see section 5.1). No data are available.

Method of administration

QINLOCK is for oral use.

The tablets should be taken at the same time each day with or without food (see section 5.2).

Prescribers should instruct patients to swallow the tablets whole and not to chew, split, or crush them. Patients should not ingest the tablets if they are broken, cracked, or otherwise not intact as the potential effects of these alterations have not been evaluated.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Palmar-Plantar Erythrodysaesthesia Syndrome (PPES)
PPES occurred in patients treated with ripretinib (see section 4.8). Based on severity, ripretinib should be withheld and then resumed at the same or reduced dose (see section 4.2).

Hypertension
Hypertension was observed with ripretinib (see section 4.8). Ripretinib must not be initiated unless blood pressure is adequately controlled. Blood pressure is to be monitored as clinically indicated. Based on severity, ripretinib should be withheld and then resumed at same or reduced dose or permanently discontinue (see section 4.2).

Cardiac failure
Cardiac failure (including cardiac failure, cardiac failure acute, acute left ventricular failure, and diastolic dysfunction) was observed with ripretinib (see section 4.8). Ejection fraction should be assessed by echocardiogram or multiple-gated acquisition (MUGA) scan prior to initiating ripretinib and during treatment, as clinically indicated. Ripretinib should be permanently discontinued for Grade

3 or 4 left ventricular systolic dysfunction (see section 4.2). The safety of ripretinib has not been assessed in patients with a baseline left ventricular ejection fraction below 50%.

Cutaneous malignancies
Cutaneous squamous cell carcinoma (CuSCC) and melanoma were reported in patients receiving ripretinib (see section 4.8). Dermatological evaluations should be performed when initiating ripretinib and routinely during treatment. Suspicious skin lesions should be managed with excision and dermatopathological evaluation. Ripretinib should be continued at the same dose.

Wound healing complications
No formal studies to evaluate the effect of ripretinib on wound healing have been conducted. Impaired wound healing complications may occur in patients who receive medicinal products that inhibit the vascular endothelial growth factor (VEGF) signalling pathway. Therefore, ripretinib has the potential to adversely affect wound healing.

Treatment with ripretinib 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. Ripretinib may then be resumed after surgery based on clinical judgement of adequate wound healing.

Embryo-foetal toxicity
Based on findings from animal studies, ripretinib can cause foetal harm when administered to pregnant women (see sections 4.6 and 5.3). It is recommended to advise women to avoid pregnancy while taking ripretinib. The pregnancy status of females of reproductive potential must be verified prior to initiating ripretinib and during treatment. Females of reproductive potential and males with female partners of reproductive potential must use effective contraception during treatment and for at least 1 week after the final dose of ripretinib (see sections 4.6 and 5.3). Effects of ripretinib on contraceptive steroids have not been studied. A barrier method contraception should be added if systemic contraceptive steroids are used.

Phototoxicity
Ripretinib exhibits a potential for phototoxicity (see section 5.3). It is recommended to advise patients to avoid or minimise exposure to direct sunlight, sunlamps, and other sources of ultraviolet radiation due to the risk of phototoxicity associated with ripretinib. Patients should be instructed to use measures such as protective clothing (long sleeves and hat) and sunscreen with high sun protection factor (SPF).

CYP3A inhibitors and inducers
Ripretinib is a CYP3A substrate. Concurrent administration of ripretinib with the strong CYP3A and P-glycoprotein (P-gp) inhibitor itraconazole resulted in an increase in ripretinib plasma exposure (see section 4.5). Caution is required when administering ripretinib with agents that are strong CYP3A and P-gp inhibitors.

Concurrent administration of ripretinib with the strong CYP3A inducer rifampicin resulted in a decrease in ripretinib plasma exposure. Therefore, chronic administration of agents that are strong or moderate CYP3A inducers with ripretinib should be avoided (see sections 4.2 and 4.5).

Important information about some excipients
QINLOCK contains lactose.

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

4.5 Interaction with other medicinal products and other forms of interaction

Both ripretinib and its active metabolite DP-5439 are mainly cleared by CYP3A4/5 and are substrates of P-gp and Breast Cancer Resistance Protein (BCRP).

Effect of other medicinal products on ripretinib

Effect of strong CYP3A/P-gp inhibitors
Co-administration of itraconazole (a strong CYP3A inhibitor) and also a P-gp inhibitor increased ripretinib C_{max} by 36% and $AUC_{0-\infty}$ by 99%. DP-5439 C_{max} was unchanged; $AUC_{0-\infty}$ increased by 99%. Strong inhibitors of CYP3A/P-gp (e.g. ketoconazole, erythromycin, clarithromycin, itraconazole, ritonavir, posaconazole, and voriconazole) are to be used with caution and patients should be monitored. Ingestion of grapefruit juice is not recommended.

Effect of CYP3A inducers
Co-administration of QINLOCK with the strong CYP3A inducer rifampicin decreased ripretinib C_{max} by 18% and $AUC_{0-\infty}$ by 61%, decreased DP-5439 $AUC_{0-\infty}$ by 57%, and increased DP-5439 C_{max} by 37%.

Concomitant use of QINLOCK with strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampicin, phenobarbital and St. John's wort) and moderate CYP3A inducers (e.g. efavirenz and etravirine) must therefore be avoided. If a strong or moderate CYP3A inducer must be co-administered, the QINLOCK dosing frequency may be increased during the co-administration period. For strong inducers, the dose may be increased from 150 mg once daily to 150 mg twice daily. For patients taking QINLOCK twice daily, if the patient misses a dose within 4 hours of the time it is usually taken, the patient should be instructed 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, the patient should be instructed not to take the missed dose and simply resume the usual dosing schedule. Monitor for clinical response and tolerability.

Effect of acid-reducing agents
No clinically significant differences in the plasma exposure to ripretinib and DP-5439 were observed when QINLOCK was co-administered with pantoprazole (a proton pump inhibitor).

Drug transporter systems
Based on *in vitro* data, medicinal products that are inhibitors of BCRP (e.g. cyclosporine A, eltrombopag) should be used with caution in combination with QINLOCK, as increased plasma concentrations of ripretinib or DP-5439 may be possible.

Effect of ripretinib on other medicinal products

CYP isoform-selective substrates
Ripretinib is a weak inhibitor of CYP2C8. Co-administration of QINLOCK with repaglinide (a sensitive index substrate for CYP2C8) increased repaglinide $AUC_{0-\infty}$ by 26%. Repaglinide C_{max} was unchanged; therefore, dose adjustment is not required.

The in vivo net effect of inhibition of CYP3A4 in the intestine and systemic CYP3A4 induction is unknown. Caution is recommended when co-administering ripretinib with sensitive CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, tacrolimus) or that are mostly metabolised in the intestine (e.g. midazolam).
Ripretinib and DP-5439 induced CYP2B6 in vitro. Co-administration of ripretinib with CYP2B6 substrates with narrow therapeutic index (e.g. efavirenz) may lead to loss of their efficacy.
Ripretinib and DP-5439 down-regulated CYP1A2 in vitro. Co-administration of ripretinib with CYP1A2 substrates with narrow therapeutic index (e.g. tizanidine) may lead to increased concentrations and monitoring is recommended.

It is unknown whether ripretinib may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a barrier method.

UGT1A substrates

In vitro studies suggested that ripretinib is an inhibitor of UGT1A1, UGT1A3, UGT1A4, UGT1A7, and UGT1A8. QINLOCK is to be used with caution in combination with clinical substrates of UGT1A enzymes (e.g. bictegravir, cabotegravir, dolutegravir, raltegravir, lamotrigine), as co-administration may lead to increased exposure of these substrates. Clinical studies with UGT1A substrates have not been conducted.

Drug transporter systems
In vitro studies suggested ripretinib is an inhibitor of P-gp and BCRP. DP-5439 is a substrate for P-gp and BCRP. DP-5439 is an inhibitor of BCRP and Multidrug And Toxin Protein 1 (MATE-1).

Medicinal products that are P-gp substrates with narrow therapeutic indices (e.g. digoxin, dabigatran etexilate) should be used with caution in combination with QINLOCK due to the likelihood of increased plasma concentrations of these substrates.

QINLOCK is to be used with caution in combination with BCRP substrates (e.g. rosuvastatin, sulfasalazine and irinotecan) and MATE-1 substrates (e.g. metformin) as co-administration of QINLOCK with BCRP and MATE-1 substrates may lead to an increase of their exposure. Clinical studies with BCRP or MATE-1 substrates have not been conducted.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Women of childbearing potential and men with female partners of reproductive potential must be informed that QINLOCK may cause foetal harm and must ensure effective contraception during treatment and for at least 1 week after the final dose of QINLOCK (see section 4.4)

The pregnancy status of females of reproductive potential is to be verified prior to initiating QINLOCK and during treatment.

Effects of QINLOCK on contraceptive steroids have not been studied. Add a barrier method if systemic steroids are used for contraception.

Pregnancy
There are no data on the use of ripretinib in pregnant women.
Based on its mechanism of action, ripretinib is suspected to cause foetal harm when administered during pregnancy and animal studies have shown reproductive toxicity (see sections 4.4 and 5.3). QINLOCK should not be used during pregnancy unless the clinical condition of the woman requires treatment with ripretinib.

Breast-feeding
It is unknown whether ripretinib/metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment with QINLOCK and for at least 1 week after the final dose.

Fertility
There are no data on the effect of ripretinib on human fertility. Based on findings from animal studies, male and female fertility may be compromised by treatment with QINLOCK (see section 5.3).

4.7 Effects on ability to drive and use machines

QINLOCK has no influence on the ability to drive and use machines. In some patients, fatigue has been reported following administration of QINLOCK. If a patient experiences fatigue, this may influence their ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

In the Phase 3 double-blind, randomised (2:1), placebo-controlled study (INVICTUS), 129 participants with a diagnosis of advanced GIST who had failed at least 3 approved prior lines of treatment were randomised to QINLOCK (n=85) or placebo (n=44) (see section 5.1). In the Phase 1 Study DCC-2618-01-001, a total of 277 patients with advanced malignancies were enrolled, and 218 patients were treated at the recommended Phase 2 dose of 150 mg QINLOCK once daily.

The median duration of treatment for QINLOCK in the double-blind period of the INVICTUS study was 5.49 months.

The most frequently observed adverse reactions (≥25%) in patients treated with QINLOCK in the pooled safety population (n=392) were fatigue (51.0%), alopecia (50.8%), nausea (39.8%), myalgia (37.8%), constipation (37.2%), diarrhoea (32.7%), PPES (29.8%), weight decreased (26.5%) and vomiting (25.8%).

The adverse reactions (≥10 to <25%) observed in patients treated with QINLOCK in the pooled safety population (n=392) were lipase increased (23.7%), muscle spasms (23.7%), arthralgia (21.2%), headache (20.7%), dyspnoea (20.2%), hypertension (19.4%), dry skin (17.6%), back pain (15.6%), cough (15.6%), blood bilirubin increased (14.0%), oedema peripheral (13.8%), hypophosphataemia (12.2%), pain in extremity (12.0%), pruritus (11.0%) and seborrhoeic keratosis (11.0%).

Grade 3/4 adverse reactions (≥2%) observed in patients treated with QINLOCK in the pooled safety population (n=392) 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%). Serious adverse reactions (≥1%) observed 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%).

Tabulated list of adverse reactions

The overall safety profile of QINLOCK is based on pooled data from 392 patients (pooled safety population) who received at least 1 dose of QINLOCK. Two clinical studies with QINLOCK in adult patients with advanced malignancies were conducted and form the primary basis of the overall evaluation of safety: a pivotal phase 3 study in adult patients with GIST, Study DCC-2618-03-001 (INVICTUS) (see section 5.1) and an open-label, first-in-human study in adult patients with advanced malignancies (Study DCC-2618-01-001).

The double-blind period of the INVICTUS study formed the primary basis of the determination of adverse reactions. The treatment emergent adverse events that were at least 5% higher in QINLOCK arm as compared to the placebo arm and those that were at least 1.5 times greater in the QINLOCK arm than those compared to placebo arm in INVICTUS were considered adverse drug reactions. Treatment emergent adverse events identified within the INVICTUS study were also evaluated across the pooled safety population (n=392). These events were considered adverse drug reactions per the Sponsor assessment. They are classified according to System Organ Class and the most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

The severity of adverse drug reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE), defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4=life threatening, and Grade 5=death.

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) and are shown in Table 2. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions reported in INVICTUS and study DCC-2618-01-001

Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Very common	Seborrhoeic keratosis
Common	Melanocytic naevus, skin papilloma, squamous cell carcinoma of skin[a], fibrous histiocytoma
Uncommon	Malignant melanoma
Endocrine disorders	
Common	Hypothyroidism
Metabolism and nutrition disorders	
Very common	Hypophosphataemia
Psychiatric disorders	
Common	Depression
Nervous system disorders	
Very common	Headache
Common	Peripheral sensory neuropathy
Cardiac disorders	
Common	Cardiac failure[b], tachycardia
Vascular disorders	
Very common	Hypertension[c]
Respiratory, thoracic and mediastinal disorders	
Very Common	Dyspnoea, cough
Gastrointestinal disorders	
Very common	Nausea, constipation, diarrhoea, vomiting
Common	Stomatitis, abdominal pain upper
Skin and subcutaneous tissue disorders	
Very common	Alopecia, PPES, dry skin, pruritus
Common	Hyperkeratosis, rash maculopapular, pruritus generalised, dermatitis acneiform
Musculoskeletal and connective tissue disorders	
Very common	Myalgia, muscle spasms, arthralgia, back pain, pain in extremity
Common	Muscular weakness, musculoskeletal chest pain
General disorders and administration site conditions	
Very common	Fatigue, oedema peripheral
Investigations	
Very common	Weight decreased, lipase increased, blood bilirubin increased
Common	Alanine aminotransferase increased

[a]Squamous cell carcinoma of skin (Squamous cell carcinoma of skin, Keratoacanthoma, Squamous cell carcinoma of head and neck)
[b]Cardiac Failure (Cardiac failure, Acute left ventricular failure, Cardiac failure acute, Diastolic dysfunction)
[c]Hypertension (Hypertension, Blood pressure increased)

Description of selected adverse drug reactions

Palmar-plantar erythrodysaesthesia syndrome (PPES)
In the double-blind period of the INVICTUS study, 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 1.2% of patients, dose interruption in 3.5% of patients, and dose reduction in 2.4% 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 week to 112.1 weeks) and 24.3 weeks (range: 0.9 week to 191.7 weeks), respectively. See sections 4.2 and 4.4 for additional information.

Hypertension

In the double-blind period of the INVICTUS study, there was a higher incidence of hypertension (all events regardless of causality) in patients treated with QINLOCK (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%. See sections 4.2 and 4.4 for additional information.

Cardiac failure
In the double-blind period of the INVICTUS study, cardiac failure (all events regardless of causality) occurred in 1.2% of the 85 patients who received QINLOCK. Cardiac failure led to dose discontinuation in 1.2% of the 85 patients who received QINLOCK.

In the pooled safety population, cardiac failure 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 left ventricular ejection fraction occurred in 2.0% of the 299 patients.

See section 4.4 for additional information.

Cutaneous malignancies
In the double-blind period of the INVICTUS study, CuSCC (all events regardless of causality) was reported in 5.9% of the 85 patients receiving QINLOCK. CuSCC of the skin was not reported in placebo-treated patients. See sections 4.2 and 4.4 for additional information.

In the pooled safety population, CuSCC occurred in 8.7% of 392 patients including Grade 3 adverse reactions in 0.5%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known specific antidote for overdose with QINLOCK.

In the event of suspected overdose, QINLOCK must be discontinued immediately, best supportive care should be initiated by a medical professional, and the patient must be observed until clinical stabilisation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other protein kinase inhibitors; ATC Code: L01EX19

Mechanism of action
Ripretinib is a novel tyrosine kinase inhibitor that inhibits KIT proto-oncogene receptor tyrosine kinase and PDGFRA kinase, including wild type, primary, and secondary mutations. Ripretinib also inhibits other kinases *in vitro*, such as PDGFRB, TIE2, VEGFR2, and BRAF.

Clinical efficacy and safety

INVICTUS (DCC-2618-03-001 study)
The efficacy and safety of QINLOCK were evaluated in a randomised (2:1), double-blind, placebo-controlled study (INVICTUS study) in patients with unresectable, locally advanced or metastatic GIST who had been previously treated with or are intolerant to at least 3 prior anticancer therapies including treatment with imatinib, sunitinib, and regorafenib. Randomisation was stratified by prior lines of therapy (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 tumour nodule within a pre-existing tumour mass must meet specific criteria to be considered unequivocal evidence of progression. Secondary efficacy endpoints included objective response rate (ORR) by BICR, overall survival (OS), and patient-reported health state, physical function (PF), and role function (RF).

Participants were randomised 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 treatment arms were unblinded 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 79 (61.2%) of patients aged 18-64 years, 32 (24.8%) of patients aged 65-74 years, and 18 (13.9%) patients aged ≥ 75 years (no patients ≥ 85 years old were randomised); male (56.6%); white (75.2%); and ECOG performance status of 0 (41.9%), 1 (49.6%), or 2 (8.5%). Sixty-three percent (63%) of patients received 3 prior therapies and approximately 37% received 4 or more prior therapies. Sixty-six percent (66%) of patients randomised to placebo crossed over to QINLOCK during the open-label period.

At the primary analysis (data cut-off date 31 May 2019) QINLOCK was compared to placebo in the INVICTUS study. QINLOCK demonstrated benefit in all assessed patient subgroups for PFS. Median PFS as determined by BICR (months) (95% CI) was 6.3 (4.6, 6.9) for QINLOCK versus 1.0 (0.9, 1.7) for placebo, HR (95% CI) 0.15 (0.09, 0.25) p-value < 0.0001. The secondary endpoint ORR (%) was 9.4 (4.2, 18) for QINLOCK versus 0 (0, 8) for placebo, p-value 0.0504 and not statistically significant. Median OS (months) (95% CI) was 15.1 (12.3, 15.1) for QINLOCK versus 6.6 (4.1, 11.6) for placebo, nominal p-value 0.0004. OS was not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints of ORR and OS.

PFS, ORR and OS results from a more recent data cut-off (10 August 2020) are shown in Table 3 and Figures 1 and 2. PFS results were similar across subgroups based on age, sex, region, ECOG status and number of previous lines of therapy.

Table 3: INVICTUS efficacy results (as of 10 August 2020)

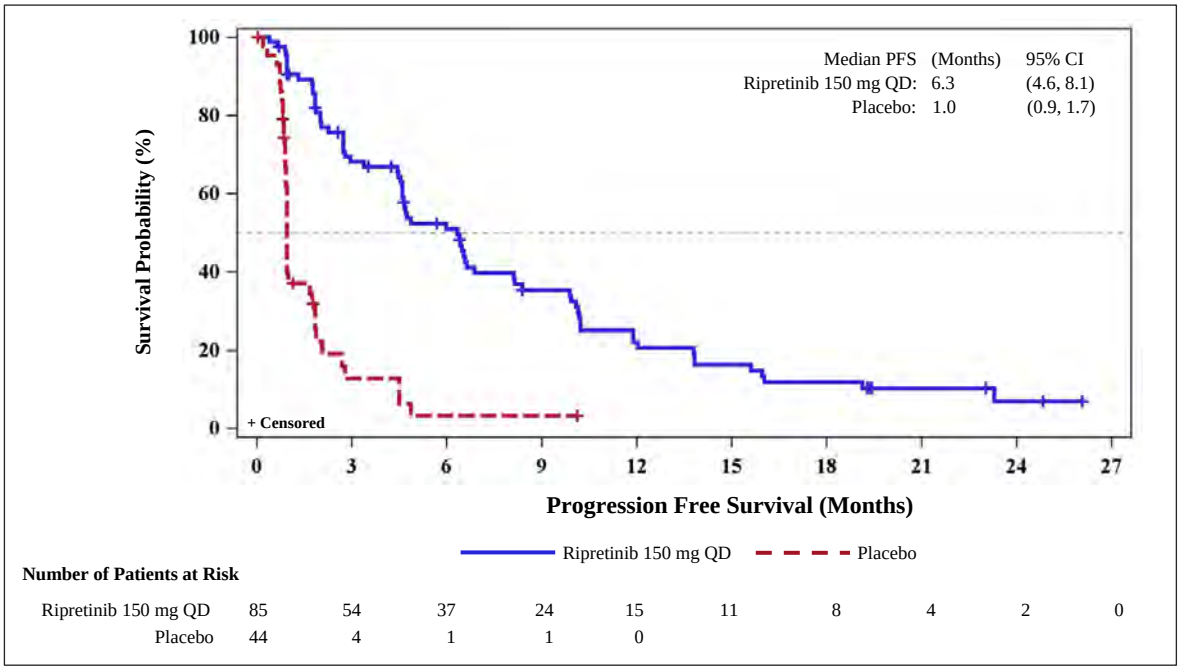
	QINLOCK (n = 85)	Placebo (n = 44)
PFS[a]		
Number of events (%)	68 (80)	37 (84)
Progressive disease	62 (73)	32 (73)
Deaths	6 (7)	5 (11)
Median PFS (months) (95% CI)	6.3 (4.6, 8.1)	1.0 (0.9, 1.7)
HR (95% CI)[b]	0.16 (0.10, 0.27)	
ORR[a]		
ORR (%)	11.8	0
(95% CI)	(5.8, 20.6)	(0, 8)
OS		
Number of deaths (%)	44 (52)	35 (80)
Median OS (months) (95% CI)	18.2 (13.1, NE)	6.3 (4.1, 10.0)
HR (95% CI)[b]	0.42 (0.27, 0.67)	

BICR = Blinded Independent Central Review; CI = Confidence Interval; HR = Hazard Ratio; ORR = Objective Response Rate; NE = not estimable; PFS = Progression Free Survival; OS = Overall Survival

[a] Assessed per BICR.

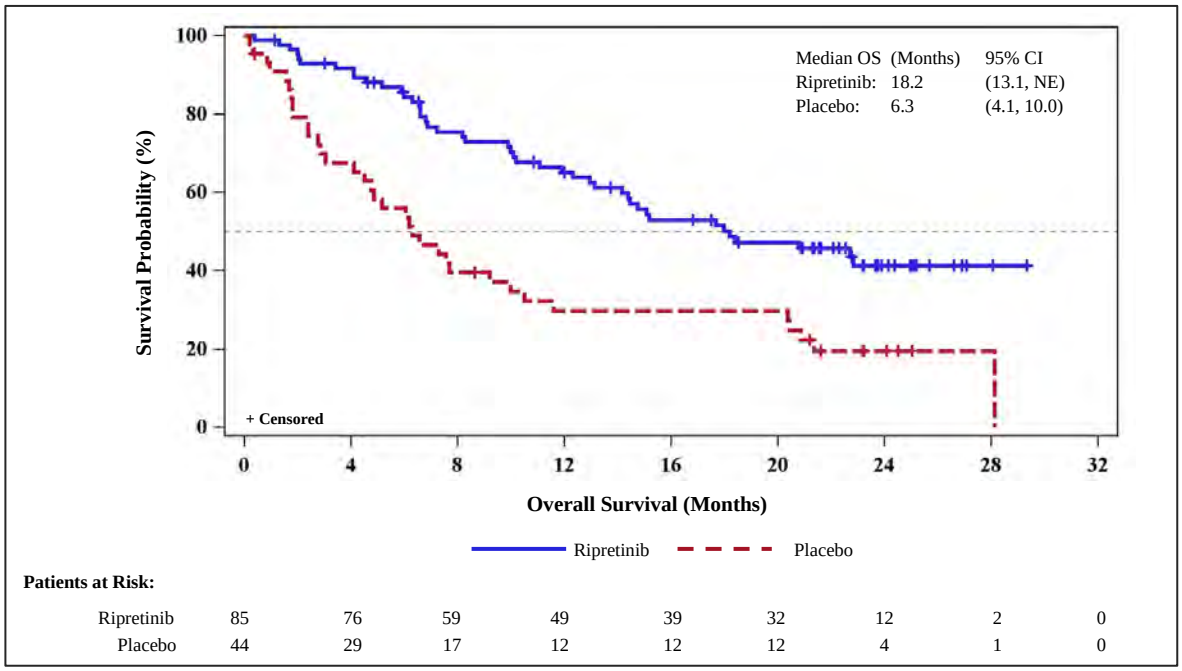
[b] Hazard ratio is based on Cox proportional regression model. This model includes treatment and randomisation stratification factors as fixed factors.

Figure 1: INVICTUS Kaplan-Meier curve of progression-free survival[a]



[a] Data cut off 10 August 2020

Figure 2: INVICTUS Kaplan-Meier curve of overall survival[a]



[a] Data cut off 10 August 2020

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with QINLOCK in all subsets of the paediatric population in the treatment of GIST (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Ripretinib reaches peak plasma concentrations at a median of 4 hours after oral administration of single dose ripretinib 150 mg (given as three tablets each containing 50 mg). The mean (CV%) $AUC_{0-\infty}$ after a single dose of 150 mg of ripretinib was 9,856 (39%) and 8,146 (56%) ng•h/mL for ripretinib and DP-5439, respectively.

Administration with a high-fat meal increased ripretinib AUC_{0-24} and C_{max} by 30% and 22%, respectively. DP-5439 AUC_{0-24} and C_{max} were higher by 47% and 66%, respectively.

Distribution

Both ripretinib and its active metabolite DP-5439 bind to plasma proteins at ≥ 99%. The mean (CV%) apparent volume of distribution (Vss/F) is approximately 302 (35%) L for ripretinib and 491 (38%) L for DP-5439.

Biotransformation

CYP3A4/5 is the major metaboliser of ripretinib and its active metabolite DP-5439, while CYP2C8 and CYP2D6 are minor metabolisers.

Elimination

Following oral administration of single dose ripretinib 150 mg in humans, mean (CV%) apparent oral clearance (CL/F) was 15.2 (39%) and 17.9 (56%) L/hr for ripretinib and DP-5439, respectively. Mean (CV%) half-life ($t_{½}$) was 12.6 (17%) and 15.6 (23%) hours for ripretinib and DP-5439, respectively.

Systemic elimination of ripretinib was not primarily attributed to the kidney with 0.02% and 0.1% of the ripretinib dose excreted as ripretinib and DP-5439, respectively, in urine and 34% and 6% of the ripretinib dose excreted as ripretinib and DP-5439, respectively, in faeces.

Dose proportionality
Across the dose range of 20-250 mg, ripretinib and DP-5439 PK appeared to be less than dose proportional, especially at ripretinib doses higher than 150 mg.

Time dependency
Steady-state conditions are achieved within 14 days.

Specific populations
No clinically significant differences in the pharmacokinetics of QINLOCK were observed based on age (19 to 87 years), sex, race (White, Black, and Asian), body weight (39 to 138 kg), and tumour (GIST or other solid tumours).

Patients with renal impairment
In clinical studies, no relevant differences in exposure were observed between patients with mild and moderate renal impairment (CLcr 30 to 89 mL/min estimated by Cockcroft-Gault) and patients with normal renal function. Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild and moderate renal impairment. The pharmacokinetics and safety of QINLOCK in patients with severe renal impairment (CLcr 15 to 29 mL/min estimated by Cockcroft-Gault) is limited. No dosing recommendation can be made in patients with severe renal impairment (see section 4.2).

Patients with hepatic impairment
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 was no impact on the pharmacokinetics of ripretinib or DP-5439. In participants with moderate hepatic impairment, ripretinib $AUC_{0\text{-tlast}}$ was approximately 99% higher while C_{max} was unchanged compared to matched healthy participants. The combined $AUC_{0\text{-tlast}}$ of ripretinib and DP-5439 was higher by approximately 51%. In participants with severe hepatic impairment, ripretinib $AUC_{0\text{-tlast}}$ was approximately 163% higher, C_{max} was approximately 24% lower, and the combined $AUC_{0\text{-tlast}}$ of ripretinib and DP-5439 was approximately 37% higher, compared to matched healthy participants. The observed magnitude of increase in ripretinib exposure is unlikely to be clinically relevant based on the known safety profile of ripretinib. Fraction of unbound ripretinib and DP-5439 was highly variable and no trend was apparent between protein binding and degree of hepatic impairment.

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

5.3 Preclinical safety data

The preclinical safety profile of ripretinib was assessed in rats and dogs for up to 13 weeks duration. Inflammation responses correlated with skin changes (discoloured, lesions) were recorded in rats (approximately 1.12 times the human exposure at 150 mg once daily). Elevated hepatic enzyme activity was reported in both species (approximately 1.12 and 1.3 times the human exposure at 150 mg once daily for rats and dogs, respectively). Dogs presented gastrointestinal effects (emesis and/or abnormal faeces) (approximately 1.3 times the human exposure at 150 mg once daily), and inflammatory responses illustrated by adverse skin lesions (approximately 0.14 times the human exposure at 150 mg once daily).

Carcinogenicity
Carcinogenicity studies have not been conducted with ripretinib.

Genotoxicity
Ripretinib was found to be positive in an *in vitro* micronucleus assay. Ripretinib was not mutagenic in *in vitro* bacterial reverse mutation (Ames) assay nor in an *in vivo* rat bone marrow micronucleus assay, demonstrating the absence of significant genotoxic risk.

Reproductive and developmental toxicity
Dedicated fertility studies in male and female animals were not conducted with ripretinib. However, in a 13-week repeat-dose toxicity study in male rats, there were findings of degeneration in the seminiferous epithelium of the testes, and cellular debris of the epididymis in males administered 30 or 300 mg/kg/day but were considered of sufficient severity to affect reproduction at dose 300 mg/kg/day only (approximately 1.4 times the human exposure at 150 mg once daily).

In a pivotal embryofoetal development study, ripretinib was teratogenic in rats, inducing dose-related malformations primarily associated with the visceral and skeletal systems at a maternal dose of 20 mg/kg/day (approximately 1.0 times the human exposure at 150 mg once daily). Additionally, skeletal variations were already observed at 5 mg/kg/day. The developmental NOAEL for ripretinib was therefore established at 1 mg/kg/day (approximately 0.02 times the human exposure at 150 mg once daily).

A study investigating effects of ripretinib on the pre-/postnatal development was not performed.

Phototoxicity
Ripretinib indicates a potential for photoirritation/phototoxicity based on absorption in the UV visible range (above 290 nm). *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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone (E1202)
Hypromellose acetate succinate
Lactose monohydrate
Magnesium stearate (E470b)
Microcrystalline cellulose (E460)
Silica, colloidal hydrated (E551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package and keep bottle tightly closed in order to protect from light and moisture.

6.5 Nature and contents of container

White high-density polyethylene (HDPE) bottle with an aluminium foil/polyethylene (PE) tamper evident seal and a white polypropylene (PP) child-resistant closure, together with one PE desiccant canister containing silica gel. Each bottle contains 30 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Deciphera Pharmaceuticals (Netherlands) B.V.
Atrium Building 4th Floor
Strawinskylaan 3051
1077ZX, Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1569/001
EU/1/21/1569/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Deciphera Pharmaceuticals (Netherlands) B.V.
Atrium Building 4th Floor
Strawinskylaan 3051
1077ZX, Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

QINLOCK 50 mg tablets
ripretinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg of ripretinib.

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep bottle tightly closed in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Deciphera Pharmaceuticals (Netherlands) B.V.
Atrium Building 4th Floor
Strawinskylaan 3051
1077ZX, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1569/001 30 tablets
EU/1/21/1569/002 90 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

QINLOCK 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

QINLOCK 50 mg tablets
ripretinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg of ripretinib.

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep bottle tightly closed in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Deciphera Pharmaceuticals (Netherlands) B.V.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1569/001	30 tablets
EU/1/21/1569/002	90 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

QINLOCK 50 mg tablets
ripretinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What QINLOCK is and what it is used for

QINLOCK is a cancer medicine containing the active substance ripretinib, a protein kinase inhibitor. Protein kinase inhibitors are used to treat cancer by stopping the activity of certain proteins that are involved in the growth and spread of cancer cells.

QINLOCK is used to treat **adults** with **gastrointestinal stromal tumour** (GIST), a rare type of **cancer of the digestive system including the stomach and bowel**, that has:
- spread to other parts of the body or cannot be removed by surgery
- been treated with at least 3 previous cancer medicines, including imatinib.

If you have any questions about how QINLOCK works or why this medicine has been prescribed for you, please ask your doctor.

2. What you need to know before you take QINLOCK

Do not take QINLOCK if you are **allergic to ripretinib** or **any of the other ingredients** of this medicine (listed in section 6).

Warnings and precautions

<u>Before taking</u> QINLOCK, talk to your doctor or pharmacist if you have or have a history of:
- high blood pressure. Your doctor will monitor your blood pressure prior to and during treatment with QINLOCK and may give you a medicine to treat high blood pressure, if needed.

- heart conditions. Your doctor may perform additional tests to assess how your heart functions prior to and during your treatment with QINLOCK.

- liver or kidney problems.

When taking QINLOCK, talk to your doctor or pharmacist if:
- you notice redness, pain, swelling, or blisters on the palms of your hands or soles of your feet. This is a skin problem called palmar-plantar erythrodysaesthesia syndrome (PPES). Your doctor may continue your treatment, change your dose or stop your treatment until your condition improves (see section 4).

- you notice unexpected skin changes such as a new wart, open sore or reddish bump that bleeds or does not heal, or a change in size or colour of a mole. QINLOCK may increase the risk of some types of skin cancers (see section 4). Your doctor will check your skin when starting treatment with QINLOCK and routinely during treatment. It is important that you check your skin regularly.

- you have wounds from any recent surgery that aren't healing as expected. QINLOCK may affect the way wounds heal. Your doctor may decide to temporarily stop treatment with QINLOCK a few days before surgery and until your wound has healed after surgery. Your doctor will decide when to start QINLOCK again. It is important that you tell your doctor if you have any planned surgeries in the future.

- you feel tired, short of breath, notice protruding veins in your neck, or have swelling of the abdomen, ankles or lower legs while taking QINLOCK, these may be symptoms of heart failure (see section 4).

- your skin or eyes become more sensitive to sunlight or other forms of light. Do not expose yourself to direct sunlight, sunlamps and other sources of ultraviolet radiation when taking this medicine. You should wear protective clothing, and apply sun cream with high sun protection factor when you are exposed to strong sunlight.

Important information for men and women about contraception
QINLOCK can cause harm to your unborn baby. **Do not** become pregnant while taking QINLOCK. Use effective contraception during treatment and for at least 1 week after the final dose of QINLOCK if you are a female of childbearing potential or a male with a female partner of childbearing potential. If using hormonal contraception, add a barrier contraception (such as condoms). See section on 'Contraception, pregnancy, breastfeeding and fertility'.

Children and adolescents
Do not give this medicine to children and adolescents below 18 years of age because it has not been studied in this age group.

Other medicines and QINLOCK
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

QINLOCK can affect the way some medicines work. Also, some medicines can affect the way QINLOCK works.

In particular, **tell your doctor** if you are taking any of the following medicines:
- medicines used to treat fungal infections (such as ketoconazole, itraconazole, posaconazole, voriconazole)
- medicines used to treat bacterial infections (such as erythromycin, clarithromycin, rifampicin)
- medicines used to treat HIV (such as ritonavir, efavirenz, etravirine, bictegravir, cabotegravir, dolutegravir, raltegravir)
- medicines used for epilepsy or fits (such as phenytoin, carbamazepine, phenobarbital, lamotrigine)
- medicines used to treat irregular heartbeats (such as digoxin)
- medicines used to prevent stroke or harmful blood clots (such as dabigatran etexilate)

- medicines used to lower elevated cholesterol (such as rosuvastatin)
- medicines used to reduce blood glucose or to treat diabetes (such as repaglinide or metformin)
- medicines used to treat severe bowel and rheumatic joint inflammation (such as sulfasalazine)
- medicines used to treat cancer (such as paclitaxel or irinotecan)
- medicines used to prevent organ rejection (such as cyclosporine, tacrolimus)
- medicines used to treat low platelet counts in the blood (such as eltrombopag)
- medicines used to treat muscle spasms (such as tizanidine)
- medicines used to relieve anxiety before procedures (such as midazolam)
- herbal preparations used to treat depression and anxiety containing St. John's Wort (*Hypericum perforatum*).

QINLOCK with food and drink
Grapefruit juice may change the amount of QINLOCK in your body. Drinking grapefruit juice or eating grapefruit is not recommended during treatment with this medicine.

Contraception, pregnancy, breast-feeding and fertility

Contraception
Both women of childbearing potential and men should use effective contraception during treatment and for at least 1 week after completion of treatment. If hormonal contraception is used, a barrier method (such as condoms) should be added.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, you should not take this medicine, unless your doctor has decided that treatment with QINLOCK is clearly necessary. Ask your doctor or pharmacist for advice before taking this medicine.

Do not get pregnant while you are being treated with QINLOCK.
If you are a male patient with a partner who is either pregnant or who could become pregnant, you must use a barrier method (such as condoms) during sexual intercourse, during treatment and for at least 1 week after completion of treatment. This medicine may harm your unborn baby.
If you are a male and your female partner becomes pregnant during your treatment with QINLOCK, tell your doctor right away.

Woman of childbearing potential will have to do pregnancy tests before treatment start with QINLOCK and during treatment.

Breastfeeding
Do not breast-feed your baby during treatment with QINLOCK and for at least 1 week after completing treatment, as this medicine may cause **serious side effects** in your baby. Tell your doctor if you are breast-feeding or planning to breast-feed.

Fertility
QINLOCK may affect fertility in men and women. Ask your doctor for advice before taking QINLOCK.

Driving and using machines
QINLOCK does not directly affect your ability to drive or use machines. If you feel unwell or very tired while being treated with QINLOCK you should not drive or operate machinery until you feel safe to do so.

QINLOCK contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take QINLOCK

QINLOCK will be prescribed for you by a doctor experienced in using anticancer therapies.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended daily dose is **three 50 mg tablets** (150 mg) once daily. **Take** the tablets at the **same time each day** with or without food. Swallow the tablets whole with a glass of water and do not chew, split, or crush the tablets. Do not take any tablets that are broken, cracked, or otherwise damaged due to unknown effects of taking tablet that are not whole.
If you have to take certain other medicines at the same time as QINLOCK, your doctor may change your dose to three 50 mg tablets (150 mg) twice daily.

You will usually take QINLOCK as long as you are benefitting from it and not suffering unacceptable side effects (see section 4); however, your doctor may reduce your dose, or may decide to interrupt or stop the treatment temporarily or permanently if necessary.

If you have kidney or severe liver problems
While you are being treated with QINLOCK, your doctor will monitor your kidney or liver function more closely.

If you take more QINLOCK than you should
If you have accidentally taken too many tablets, **seek urgent medical attention.**

If you forget to take QINLOCK
What to do if you forget to take this medicine, depends on when you remember the dose that has been forgotten. If it is:
- 8 hours or less (4 hours or less for 150 mg twice per day doses) after the time it should have been taken, take the missed dose as soon as you remember. Then take the next dose as usual.
- more than 8 hours after (more than 4 hours for 150 mg twice per day doses) the time it should have been taken, skip the missed dose. Then take the next dose at the usual time.

Do not take a double dose to make up a forgotten dose.

If you are sick when taking QINLOCK
If you are sick (vomiting) after taking this medicine, **do not** take an additional dose, but carry on as normal. Take your next dose of tablets the next day at the usual time and tell your doctor you have been sick.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Seek urgent medical attention if you experience any of the following **serious side effects** (see section 2):
- **Skin problems** (called PPES)
  PPES is a very common side effect when taking this medicine. If you develop:
  - redness, pain, swelling, or blisters on the palms of your hands or soles of your feet,

your doctor may continue your treatment, change your dose or stop your treatment until your condition improves.

- **High blood pressure**
  High blood pressure is a very common side effect when taking this medicine. If you develop:

- headache, feeling of lightheadedness, or dizziness, these may be symptoms of high blood pressure,

your doctor may change your dose or stop your treatment until your condition improves.

- **Heart problems (heart failure)**
  Heart failure is a common side effect when taking this medicine. If you feel:
  - very tired, are short of breath, have swollen feet and/or ankles,

these may be symptoms of heart problems.

Talk to your doctor or pharmacist if you experience:

- **Skin cancer**
  Treatment with QINLOCK may result in certain types of skin cancer such as 'cutaneous squamous cell carcinoma' and 'melanoma'. Tell your doctor if you notice any skin changes during treatment including a new wart, open sore or reddish bump that bleeds or does not heal, or a change in size or colour of a mole. Your doctor will check your skin when starting treatment with QINLOCK and routinely during treatment (see section 2).

Very common side effects (may affect more than 1 in 10 people):
- feeling sick (nausea)
- constipation
- diarrhoea
- being sick (vomiting)
- joint pain
- headache
- shortness of breath
- blood tests showing increased levels of bilirubin, a substance produced by the liver
- blood tests showing increased levels of lipase, an enzyme involved in digestion
- blood tests showing decreased levels of phosphate
- tiredness
- hair loss
- muscle ache or pain
- weight loss
- muscle spasms
- dry skin
- back pain
- cough
- swelling in hands and lower legs
- pain in hands or feet
- itching
- non-cancerous skin lesions

Common side effects (may affect up to 1 in 10 people):
- sores in mouth
- belly (abdominal) pain
- peripheral nerve impairment (numbness and tingling in feet or hands, burning, stabbing or shooting pain in affected areas, loss of balance and co-coordination, and muscle weakness, especially in the feet)
- skin reactions such as flaking and inflammation of the skin, rash characterised by a flat, red area on the skin that is covered with small bumps or acne
- abnormal liver test (possible liver damage shown by blood test)
- depression
- underactive thyroid gland
- weakness
- chest pain
- rapid heart rate

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store QINLOCK

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

Store in the original package and keep the bottle tightly closed in order to protect from light and moisture.

Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What QINLOCK contains
- The active substance is ripretinib. Each tablet contains 50 mg of ripretinib.
- The other ingredients are crospovidone (E1202), hypromellose acetate succinate, lactose monohydrate, magnesium stearate (E470b), microcrystalline cellulose (E460), and colloidal hydrated silica (E551) (see section 2 “QINLOCK contains lactose”).

What QINLOCK looks like and contents of the pack
QINLOCK tablets are white to off-white, oval in shape, and debossed with ‘DC1' on one side.

Each bottle is child-resistant and contains 30 or 90 tablets and a desiccant. The bottles are provided with aluminium foil/polyethylene (PE) tamper evident seal. The desiccant is a moisture absorbing material filled in a small container to protect the tablets from moisture. Always keep the desiccant pouch in the bottle and do not eat it.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Deciphera Pharmaceuticals (Netherlands) B.V.
Atrium Building 4th Floor
Strawinskylaan 3051
1077ZX, Amsterdam
Netherlands

Manufacturer
Deciphera Pharmaceuticals (Netherlands) B.V.
Atrium Building 4th Floor
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1077ZX, Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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