SUMMARY OF THE RISK MANAGEMENT PLAN

FOR

QINLOCK (RIPRETINIB)

Deciphera Pharmaceuticals (Schweiz) AG

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of QINLOCK is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of QINLOCK in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Deciphera Pharmaceuticals AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of QINLOCK.

I. The medicine and what it is used for

QINLOCK is authorized for the treatment of adult patients with advanced gastrointestinal stromal tumours (GIST) who have received at least 2 or more kinase inhibitors therapies (see Product Information for the full indication). It contains ripretinib as the active substance and it is given orally.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of QINLOCK, together with measures to minimize such risks and the proposed studies for learning more about QINLOCK's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety updated report (PSUR) assessment - so that immediate action can be taken, as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of QINLOCK is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of QINLOCK are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of QINLOCK. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Palmar-plantar erythrodysaesthesia syndrome Hypertension Cardiac dysfunction
Important potential risks	Squamous cell carcinoma of skin Embryo-foetal toxicity
Missing information	Use in patients with moderate or severe hepatic impairment Use in patients with severe renal impairment

II.B Summary of important risks

Important identified risk: Palmar-plantar erythrodysaesthesia	
Evidence for linking the risk to the medicine	Palmar-plantar erythrodysaesthesia syndrome (PPES) also known as hand-foot skin reaction (HFSR) is a common adverse reaction of TKIs. In Study DCC-2618-03-001, PPES occurred in 21.2% (18 of 85) of patients treated with ripretinib 150 mg daily. All events were mild or moderate in severity. PPES was not seen in patients treated with placebo in the study. Non-clinical studies also showed signs of potential adverse effects on skin (300 mg/kg/day in rats and 10 mg/kg/day in dogs). Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. Nonclinical findings may be relevant for humans and in the absence of clinical data suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Some cancer therapies, including tyrosine kinase inhibitors, are recognized to cause PPES and therefore patients treated with these therapies are at increased risk. Patients whose jobs require a significant amount of walking or hand friction are at greater risk of developing these skin toxicities and use of caustic cleaning solutions and hot water are also contributors. The severity of PPES is related to pressure, friction and heat, and tends to be more severe in younger, 'more-active' patients.
Risk minimisation measures	Routine risk minimisation measures: • *Dose modifications for Grade 2 and Grade 3 PPES in SmPC Section 4.2* • *Treatment guidance in SmPC Section 4.4 and in package leaflet section 4* • *SmPC Section 4.8* • *Package leaflet section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Important identified risk: Hypertension	
Evidence for linking the risk to the medicine	Hypertension occurred in 14.1% (12 of 85) of patients treated with ripretinib 150 mg daily and 4.7% (2 of 43) of patients treated with placebo in Study DCC-2618-03-001. Hypertension was severe (Grade 3) in 6 (7.1%) patients treated with ripretinib. Nonclinical studies also suggested an effect on blood pressure. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. Nonclinical findings may be relevant for humans and in the absence of clinical data suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	The potential risk group for hypertension or its complications are patients with uncontrolled hypertension. Other risk factors for hypertension include increased age, a family history of hypertension, African heritage, increased weight or obesity, physical inactivity, tobacco use, high salt intake and low potassium dietary intake, increased alcohol consumption, stress, and certain chronic conditions including kidney disease, diabetes, and sleep apnoea.
Risk minimisation measures	Routine risk minimisation measures: • *Dose modifications and medical management of Grade 3 hypertension and to permanently discontinue ripretinib for Grade 4 hypertension in SmPC Section 4.2* • *Warning on the actions to take in SmPC Section 4.4*

	• *SmPC Section 4.8* • *Package leaflet section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Important identified risk: Cardiac Dysfunction	
Evidence for linking the risk to the medicine	Tyrosine kinase inhibitors are recognised to cause cardiac dysfunction. Cardiac failure occurred in 1.2% (1 of 85) of patients treated with ripretinib 150 mg daily during the double-blind treatment period in Study DCC-2618-03-001 and none in placebo treated patients. The event was of Grade 3 severity. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Risk factors and risk groups	Patients with a history of cardiac disease appear to be at increased risk, a population that should be under constant monitoring for their underlying condition. Risk factors for cardiac failure include hypertension, coronary artery disease, myocardial infarction, diabetes, sleep apnoea, congenital heart defects, valvular heart disease, viral infection, alcohol use, tobacco use, obesity, and irregular heartbeats. Certain medications may lead to cardiac failure including diabetes medications rosiglitazone (Avandia) and pioglitazone (Actos), nonsteroidal anti-inflammatory drugs (NSAIDs); certain anaesthesia medications; some anti-arrhythmic medications; certain medications used to treat high blood pressure, cancer, blood conditions, neurological conditions, psychiatric conditions, lung conditions, urological conditions, inflammatory conditions and infections; and other prescription and over-the-counter medications . Tyrosine kinase inhibitors are recognised to cause cardiac dysfunction and therefore patients treated with these therapies are at increased risk.
Risk minimisation measures	Routine risk minimisation measures: • *Guidance to discontinue ripretinib in case of Grade 3 or 4 left ventricular systolic dysfunction in SmPC Sections 4.2 and 4.4* • *Warning to assess ejection fraction prior to initiating ripretinib and during treatment as clinically indicated in SmPC Section 4.4* • *SmPC Section 4.8* • *Package leaflet section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Important potential risk: Squamous cell carcinoma of skin	
Evidence for linking the risk to the medicine	Squamous cell carcinoma of skin occurred in 4.7% (4 of 85) of patients treated with ripretinib 150 mg daily and in no patients treated with placebo in Study DCC-2618-03-001. All of these patients experienced Grade 2 intensity squamous cell carcinoma of skin. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.

Risk factors and risk groups	The most common risk factor for squamous cell carcinoma is ultraviolet radiation which frequently produces point mutations in double-stranded DNA, resulting in the formation of thymidine dimers in the p53 tumour-suppressor gene. Failure of repair mechanisms may then lead to tumour formation. Squamous cell carcinoma has also been associated with immunosuppression, arsenic exposure, radiation, chronic ulcers, human papillomavirus (HPV) infection, and tyrosine kinase inhibitors such as imatinib mesylate.
Risk minimisation measures	Routine risk minimisation measures: • *Warning for patients to receive dermatological examinations when initiating ripretinib and routinely during treatment and on the actions to take in SmPC Section 4.4 and in package leaflet section 4* • *Warning to manage suspicious skin lesions with excision and dermatopathological evaluation in SmPC Section 4.4* • *SmPC Section 4.8* • *Package leaflet section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	There are no data available for ripretinib exposure in pregnant women. Use of ripretinib during pregnancy has not been evaluated in the clinical development programme. In animal embryo-foetal toxicity studies ripretinib was teratogenic in rats, with malformations observed in the cardiovascular and skeletal systems. Nonclinical findings may be relevant for humans and in the absence of clinical data suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Women of childbearing potential and male patients with female partners of reproductive potential not using a reliable method of contraception during treatment with ripretinib and for at least 4 months after the final dose are at risk of embryo-foetal toxicity.
Risk minimisation measures	Routine risk minimisation measures: • *Warning that ripretinib should not be used during pregnancy, to verify the pregnancy status prior to initiating ripretinib, and to use effective contraception during treatment and for at least 4 months after the final dose in SmPC Sections 4.4 and 4.6 and in package leaflet section 2* • *Information on non-clinical findings in SmPC Section 5.3* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Missing information: Use in patients with moderate or severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • *Information that pharmacokinetics and safety in patients with moderate or severe hepatic impairment have not been studied and that no dosing recommendation can be made in this subgroup in SmPC Sections 4.2 and in package leaflet section 3* • *Guidance to closely monitor the overall safety in patients with moderate and severe hepatic impairment in SmPC Section 4.2* • *Information that the impact of moderate or severe hepatic impairment on the pharmacokinetics of ripretinib is unknown in SmPC Section 5.2* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study DCC-2618-01-004* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: • *Information that pharmacokinetics and safety in patients with severe renal impairment have not been studied and that no dosing recommendation has been established for patients with severe renal impairment in SmPC Section 4.2 and in package leaflet section 3* • *Information that the impact of severe renal impairment on the pharmacokinetics of ripretinib is unknown in SmPC Section 5.2* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ripretinib.

II.C.2 Other studies in post-authorisation development plan

Study DCC-2618-01-004

Purpose of the study:

To investigate the impact of mild, moderate, and severe hepatic impairment on ripretinib PK.

To assess the PK, safety, and tolerability of a single 50 mg dose of ripretinib in subjects with hepatic impairment compared to matched healthy subjects with normal hepatic function.