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.

Summary of the risk management plan for QINLOCK

This is a summary of the risk management plan (RMP) for QINLOCK. The RMP details important risks of QINLOCK, how these risks can be minimised, and how more information will be obtained about QINLOCK's risks and uncertainties (missing information).

QINLOCK's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how QINLOCK should be used.

This summary of the RMP for QINLOCK should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of QINLOCK's RMP.

I. The medicine and what it is used for

QINLOCK is authorised for the treatment of adult patients with advanced gastrointestinal stromal tumours (GIST) who have received at least 3 or more kinase inhibitors including imatinib (see Product Information for the full indication). It contains ripretinib as the active substance and it is given orally.

Further information about the evaluation of QINLOCK's benefits can be found in QINLOCK's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/qinlock.

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

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

Measures to minimise 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 authorised 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 minimise 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 failure
Important potential risks	Embryo-foetal toxicity Phototoxicity
Missing information	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 22.4% (19 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 (Smith and Abou-Alfa, 2010). The severity of PPES is related to pressure, friction and heat, and tends to be more severe in younger, ‘more-active’ patients (Edmonds et al., 2012).
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 15.3% (13 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 (Mayo Clinic, 2019).
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 Failure	
Evidence for linking the risk to the medicine	Tyrosine kinase inhibitors are recognised to cause cardiac dysfunction. Cardiac failure events 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. All of 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 (Mayo Clinic, 2020). 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 (Mayo Clinic, 2020). 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 Section 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: 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	Females of childbearing potential and males with partners of reproductive potential must be informed that QINLOCK may cause foetal harm, and must ensure effective contraception during treatment and at least 1 week after the final dose of QINLOCK
Risk minimisation measures	Routine risk minimisation measures: • *Recommendation to advise women to avoid pregnancy while taking ripretinib unless clearly necessary, to verify the pregnancy status prior to initiating ripretinib and during the treatment, and to use effective contraception during treatment (with a barrier method of contraception if systemic contraceptive steroids are used) for at least 1 week after the final dose in SmPC Section 4.4 and Section 4.6 and in package leaflet section 2* • *Information on non-clinical findings in Section 5.3* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Important potential risk: Phototoxicity	
Evidence for linking the risk to the medicine	The nonclinical data suggested that ripretinib and metabolite DP-5439 exhibit the potential for ultraviolet (UV)-induced phototoxicity in an *in vitro* assay. In integrated analysis pool 3 data only 1% (4 of 392) of patients experienced adverse events related to photosensitivity. Majority (3 of 4) of these patients (0.8%, 3 of 392) experienced mild events; and only 1 patient (0.2%) experienced event of moderate intensity. None of the photosensitivity events were considered as serious or were reported with severe intensity. 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 significant clinical data suggest a potential safety concern that needs further clinical confirmation.
Risk factors and risk groups	No major risk factors were identified. However, patient's exposure to strong sunlight, sunlamps, and other sources of ultraviolets radiation and the absence of prophylactic skin care (e.g., SPF $\geq$ 30, hypoallergenic moisturizing creams or ointments for dry skin, and gentle skincare with fragrance-free soaps and detergents) can increase the chances of occurrence of photosensitivity reactions.

Risk minimisation measures	Routine risk minimisation measures: • *Recommendation to 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; and advise patients to use measures such as protective clothing (long sleeves and hat) and sunscreen with high SPF in SmPC Section 4.4 and in package leaflet section 2* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: • *Information that only limited clinical data are available in patients with severe renal impairment (CLcr <30 mL/min) and that a recommended dose of ripretinib has not been established in patients with severe renal impairment in SmPC Section 4.2 and 5.2 and in package leaflet section 3* • *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

There are no studies required for QINLOCK.

References for the RMP Summary

Edmonds K, Hull D, Spencer-Shaw A, Koldenhof J, Chrysou M, Boers-Doets C, et al. Strategies for assessing and managing the adverse events of sorafenib and other targeted therapies in the treatment of renal cell and hepatocellular carcinoma: recommendations from a European nursing task group. Eur J Oncol Nurs. 2012; 16: 172-84.

Mayo Clinic. Heart failure. (Internet) Available at https://www.mayoclinic.org/diseases-conditions/heart-failure/symptoms-causes/syc-20373142 Accessed 18 May 2020. [Mayo Clinic, 2020]

Mayo Clinic. High blood pressure (hypertension). (Internet) Available at https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/symptoms-causes/syc-20373410 Accessed 03 Dec 2019. [May Clinic 2019]

Smith W and Abou-Alfa GK. Nursing management of hand-foot syndrome and hand-foot skin reaction. Lab Med J. 2010; 58-A: S63-5.