Regulatory Affairs

KISQALI®

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Ribociclib
Product(s) concerned (brand name(s)):	KISQALI®
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Summary of the risk management plan for Kisqali® (Ribociclib)

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 Kisqali® 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 Kisqali® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Kisqali®.

I. The medicine and what it is used for

KISQALI® is authorised for the treatment of patients with HR+/HER2- locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant (see SmPC for the full indication). It contains ribociclib as the active substance**,** it is given by oral route and is used in combination with letrozole to treat postmenopausal women with HR-positive, HER2- negative breast cancer when the disease is locally advanced or spread to other parts/organs of the body as initial hormone-based therapy. Additional details on the approved indication are available in the SmPC.

Route of administration, pharmaceutical forms and strengths:

KISQALI® is available as 200 mg film-coated tablets for oral administration. Additional details on the approved information on route of administration are available in the SmPC.

Further information about the evaluation of KISQALI® benefits can be found in KISQALI® EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004213/WC500234000.pdf (last accessed: 21-09-2018).

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

Important risks of KISQALI® studies for learning more about KISQALI® 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 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 minimize its risks. "Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication."

Together, these measures constitute routine risk minimization measures.

In the case of KISQALI®, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 KISQALI® is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of KISQALI® are risks that need special risk management activities to furtherinvestigate or minimize the risk, so that the medicinal product can be safely administered. 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 KISQALI®. 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);

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Myelosuppression Hepatobiliary toxicity QT interval prolongation Reproductive Toxicity
Important potential risks	Renal toxicity Interstitial Lung Disease (ILD) / pneumonitis
Missing information	Safety in Japanese patients Safety in male patients with breast cancer Long-term use

II B: Summary of important risks

Table 2 Important identified risk - Myelosuppression

Evidence for linking the risk to the medicine	Bone marrow hypocellularity was predicted by preclinical studies and is considered to be related to the pharmacological inhibition of cell replication due to CDK4/6 inhibition. Neutropenia has been the most common toxicity observed in clinical practice. Grade 3 or 4 neutropenia including febrile neutropenia has been reported as dose-limiting toxicities in single-agent ribociclib trials.
Risk factors and risk groups	Patients with low baseline neutrophil and/or leukocyte counts.
Risk minimization measures	**Routine risk minimization measures:** Addressed in Section 4.2, Section 4.4 and Section 4.8 of the SmPC **Additional risk minimization measures**: None

Table 3 Important identified risk - Hepatobiliary toxicity

Evidence for linking the risk to the medicine	Hepatobiliary toxicity has been reported during treatment with ribociclib and therefore, should be closely monitored. Preclinical data have reported fully reversible proliferative changes consistent with hepatobiliary toxicity. Specifically in dogs: the liver, the biliary system and the gallbladder showed proliferative changes, cholestasis, sand-like gallbladder calculi and thickening bile. These changes are not likely related to the primary pharmacology of ribociclib. The changes observed in the liver were mainly driven by the biliary duct system with, most likely, "bystander" effects on the surrounding hepatocytes and vasculature (i.e. locally irritating with additional cholestasis).
Risk factors and risk groups	There are no identified risk factors for the occurrence of hepatotoxicity (including liver laboratory abnormalities and DILI) in ribociclib-treated patients. Common causative/risk factors for hepatotoxicity include: • Elderly patients are at increased risk of hepatic injury due to reduced blood flow to the liver, drug-drug interactions (DDIs), and decreased drug clearance. • Alcohol abuse in patients with cirrhotic liver changes • Concomitant use of hepatotoxic medications.
Risk minimization measures	**Routine risk minimization measures**: Addressed in Section 4.2, Section 4.4, Section 4.8, and Section 5.3 of the SmPC. **Additional risk minimization measures**: None

Table 4 Important identified risk - QT interval prolongation

Evidence for linking the risk to the medicine	In vivo cardiac safety studies in dogs demonstrated a signal for QT prolongation at an exposure expected to be achieved in patients following the recommended dose of 600 mg with the potential to induce incidences of PVCs at higher exposure levels (approximately 5-fold the achieved clinical Cmax). There were no effects on heart rate, blood pressure, core body temperature, or other ECG findings.
Risk factors and risk groups	Patients with history of cardiac disease, electrolyte imbalances (hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia), and concomitant intake of QT-prolonging drugs. The co-administration of medications that may increase the risk of QTc prolongation such as strong CYP3A4 inhibitors; and medications that have a known risk for QT prolongation.
Risk minimization measures	**Routine risk minimization measures**: Addressed in Section 4.2, Section 4.4, Section 4.5, Section 4.8, Section 5.1 and Section 5.3 of the SmPC **Additional risk minimization measures:** None

Table 5 Important identified risk – Reproductive Toxicity

Evidence for linking the risk to the medicine	Based on findings in animals and mechanism of action, ribociclib can cause fetal harm when administered to a pregnant woman. Ribociclib caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below and 1.5 times the human clinical exposure based on area under the curve (AUC). Based on animal studies, ribociclib may impair fertility in males of reproductive potential.
Risk factors and risk groups	Women of childbearing age becoming pregnant and/or requiring treatment with ribociclib through pregnancy.
Risk minimization measures	**Routine risk minimization measures**: Addressed in Section 4.4, Section 4.6 and Section 5.3 of the SmPC. **Additional risk minimization measures**: None

Table 6 Important Potential risk - Renal toxicity

Evidence for linking the risk to the medicine	Reversible degeneration of the kidney tubular epithelial cells has been observed in the 15-week rat toxicity study. Cases of creatinine increase have been reported in clinical studies.
Risk factors and risk groups	Patients with severe renal dysfunction Patients with severe dehydration.
Risk minimization measures	**Routine risk minimization measures** Addressed in Section 4.2, Section 4.8 and Section 5.2 of the SmPC **Additional risk minimization measures**: None

Table 7 Important Potential risk - Interstitial Lung Disease (ILD) / pneumonitis

Evidence for linking the risk to the medicine	ILD/Pneumonitis is seen as a class effect of CDK4/6 inhibitors. Cases of ILD/Pneumonitis have been reported with ribociclib in clinical studies and in the post-marketing setting.
Risk factors and risk groups	There are no identified risk factors for the occurrence of ILD/Pneumonitis in ribociclib-treated patients. Common causative/risk factors for ILD/Pneumonitis include: • Chemo- and radiotherapy • Therapy with medications known to cause pulmonary toxicity in the past or concurrently • Smoking, including e-cigarettes • Genetic susceptibility (e.g. Japanese patients, and this may be a combination of genetic susceptibility and variation in reporting, which has been observed between different countries)
Risk minimization measures	**Routine risk minimization measures** Proposed text in the SmPC (Section 4.2 and Section 4.4) addresses the risk in the patient population. **Additional risk minimization measures**: None

Table 8 Missing information - Safety in Japanese patients

Risk minimization measures	**Routine risk minimization measures**: None **Additional risk minimization measures**: None

Table 9 Missing information - Safety in male patients with breast cancer

Risk minimization measures	**Routine risk minimization measures**: None **Additional risk minimization measures**: None

Table 10 Missing information - Long-term use

Risk minimization measures	**Routine risk minimization measures**: None **Additional risk minimization measures**: None
Additional pharmacovigilance activities	**Study CLEE011A2301 (MONALEESA-2):** A randomized double-blind, placebo-controlled Phase III study of ribociclib in combination with letrozole for the treatment of postmenopausal women with HR+, HER2-negative advanced breast cancer who received no prior therapy for advanced disease.

II C: Post-authorization development plan

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

There are no conditions to the marketing authorization of ribociclib.

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

Table 11 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CLEE011A2301 (MONALEESA-2):	**Rationale**: To assess long term use. **Study objectives:** To compare PFS between ribociclib in combination with letrozole to placebo plus letrozole among postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for their advanced breast cancer.