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®*
Document status:	*Final*
Version number of the RMP Public Summary:	*V8.1*
Date of final sign off of the RMP Public Summary	*10-Apr-2025*

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”.

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Summary of the risk management plan for KISQALI® (ribociclib)

This is a summary of the risk management plan (RMP) for KISQALI®. The RMP details important risks of KISQALI®, how these risks can be minimized, and how more information will be obtained about KISQALI® risks and uncertainties (missing information).
KISQALI® summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how KISQALI® should be used.
This summary of the RMP for KISQALI® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates to the KISQALI® RMP.

I. The medicine and what it is used for

KISQALI® is authorised for:

- Treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.
- Adjuvant treatment of patients with HR-positive, HER2-negative stage II and III early breast cancer, irrespective of nodal status, in combination with an aromatase inhibitor. In pre- or perimenopausal women, or men, the aromatase inhibitor should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Additional details on the both the indications 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.

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

Important risks of KISQALI® together with measures to minimize such risks and the proposed studies for learning more about KISQALI®'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 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.
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 further investigate 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
Missing information	Safety in Japanese patients

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 and Section 2 of PL. **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 and Section 2 of PL. **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 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 and Section 2 of PL. **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 and Section 2 of PL. **Additional risk minimization measures**: None

Table-6 Important identified 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. The endogenous marker, cystatin C, was measured to further investigate renal function, and no obvious changes in cystatin C levels were observed following a single 400 mg dose of ribociclib, suggesting ribociclib does not cause direct renal toxicity (Study A2116 Interim report Part 1 dated 02-Feb-2018).
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 Missing information – Safety in Japanese patients

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

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

None.