Summary of the Risk Management Plan (RMP) for

Rubraca® (Rucaparib)

RMP Summary: Version 7.0, dated 11 November 2022

Disclaimer:

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 Rucaparib 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 Rucaparib in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Clovis Oncology Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Rucaparib.

Summary of risk management plan for Rubraca (Rucaparib)

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

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

This summary of the RMP for Rubraca 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 Rubraca's RMP.

I. The medicine and what it is used for

Rubraca is as authorised for monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. It contains rucaparib as the active substance and it is given by oral administration.
Further information about the evaluation of Rubraca's benefits can be found in Rubraca's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/medicines/human/EPAR/rubraca).

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

Important risks of Rubraca, together with measures to minimise such risks and the proposed studies for learning more about Rubraca'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 Update 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 Rubraca is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Rubraca are risks that need special risk management activities to further investigate or minimise 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 Rubraca. 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).

Summary of important risks and missing information	
Important identified risks	None
Important potential risks	MDS/AML New primary malignancy QTc interval prolongation Embryotoxicity and teratogenicity
Missing information	Safety in patients with severe renal impairment Safety in patients with moderate hepatic impairment

II.B Summary of important risks

Important potential risk 1: MDS/AML	
Evidence for linking the risk to the medicine	During clinical development, some events of MDS/AML were reported. However, there is insufficient scientific evidence to conclude that the cases of MDS and AML were causally related to rucaparib. MDS/AML is serious, potentially life-threatening and would require medical intervention and hence it is an important potential risk.
Risk factors and risk groups	Therapy-related myeloid leukaemia and MDS are recognised clinical syndromes, which are complications of cytotoxic therapy.[27] Therapy-related leukaemia is a complication of chemoradiotherapy used to treat a variety of primary malignancies including ovarian cancer.[50] Travis et al reported a case-control study of secondary leukaemia in a population-based cohort in North America and Europe. Between 1980 and 1993, 28,971 patients with invasive ovarian cancer were followed.[28] It was concluded that platinum-based treatment increases the risk of secondary leukaemia in patients with ovarian cancer. Among the patients who received platinum-based combination chemotherapy, the RR of leukaemia was 4.0 (95% CI, 1.4-11.4). In a Danish study of newly diagnosed ovarian cancer cases between 2000 and 2011, any other concomitant cancer was the most prevalent co-morbidity, registered in 7.9% (121) of the ovarian cancer patients.[22] Recently, in the placebo arm of a randomised, Phase 3 maintenance study of niraparib in patients who had received two or more previous lines of cytotoxic chemotherapy, MDS/AML occurred in 1.2% of patients.[51,52] The majority of patients with AML and MDS are elderly. Based on data from the Haematological Malignancy Research Network, in a cohort of patients with a newly diagnosed haematological malignancy, between 2004 and 2009, the median age at diagnosis for AML and MDS was 68.7 and 76.1 years, respectively. These diseases are more common in men. The sex-rate ratio (male/female) for AML and MDS was 1.25 (95% CI, 1.07–1.45) and 2.09 (95% CI, 1.78–2.48), respectively.[53] Obesity is a risk factor for AML. In a meta-analysis of prospective cohort studies, seven studies reported on the correlation between

	AML and BMI. Obesity was associated with a significantly increased incidence of AML (RR = 1.53; 95% CI, 1.26–1.85; p < 0.001).[54] There were 5 TEAEs leading to death in the tBRCA population treated with rucaparib. Of these, 4 occurred in the gBRCA group and 1 occurred in a patient for whom the germline/somatic status was unknown. Three of these TEAEs were assessed as not related to rucaparib, including 2 of the TEAEs within the germline subgroup (malignant neoplasm progression [n=1] and cardiac arrest [n=1]) and 1 within the germline/somatic unknown group (histiocytosis haematophagic). Within the gBRCA group, there were TEAEs of AML and MDS that led to death (n=1 each). Both patients had received multiple regimens and cycles of prior chemotherapy, including platinum- and/or taxane-containing regimens. While there appeared to be a difference within the gBRCA population as compared to those with somatic or unknown germline/somatic BRCA status, the TEAEs leading to death were either assessed as unrelated to rucaparib or, for the TEAEs of MDS and AML, the causality was confounded by the exposure to prior chemotherapy. Despite the very small number of patients involved, it remains possible/plausible that patients with gBRCA mutations are more likely to develop (fatal) haematological malignancies.
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.4, 4.8* *PL section: 2* *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Important potential risk 2: New primary malignancy	
Evidence for linking the risk to the medicine	Secondary malignancy is consistent with the known outcomes of immunosuppression resulting from chemotherapy. During clinical development, some events of new primary malignancy were reported. However, these events were either deemed not related to rucaparib or there were confounding factors such as other chemotherapy agents. New primary malignancy is serious, potentially life-threatening and would require medical intervention and hence it is an important potential risk.
Risk factors and risk groups	Prior DNA-damaging chemotherapeutic drugs represents a risk factor for development of new malignancies.[55]
Risk minimisation measures	**Routine risk minimisation measures**: *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance	**Additional pharmacovigilance activities**: *None*

activities	

Important potential risk 3: QTc interval prolongation	
Evidence for linking the risk to the medicine	In vitro studies showed that rucaparib at high concentrations may interfere with the activity of the hERG potassium channels and thus has the potential to induce QTc interval prolongation. An open-label single-arm study in 56 patients showed that a clinically significant QTcF increase (ie > 20 msec) over baseline is unlikely following administration of 600 mg BID rucaparib. During clinical development, there were a few events that were associated with the QT prolongation but all were confounded by other factors. QTc interval prolongation is serious, potentially life-threatening event and hence it is an important potential risk.
Risk factors and risk groups	Patients with certain congenital and or acquired cardiac abnormalities may be at risk of QTc prolongation. Additionally, factors that predispose to QT prolongation and higher risk of torsades de pointes include older age, female sex, low left ventricular ejection fraction, left ventricular hypertrophy, ischaemia, slow hear rate, and electrolyte abnormalities including hypokalaemia and hypomagnesemia. Certain drugs also predispose to QT prolongation. [56]
Risk minimisation measures	**Routine risk minimisation measures**: *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Important potential risk 4: Embryotoxicity and Teratogenicity	
Evidence for linking the risk to the medicine	There were no reports of embryotoxicity or teratogenicity during clinical development.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.4, 5.3* *PL section: 2* *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Missing information 1: Safety in patients with severe renal impairment	
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.2, 5.2* *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Missing information 2: Safety in patients with moderate hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.2, 5.2* *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation
The following studies are conditions of the marketing authorisation:

Study name	**Rationale and study objectives**
CO-338-014 (ARIEL3)	Primary: To compare the anti-tumour efficacy of oral single agent rucaparib with that of placebo as measured by PFS, when administered as a switch maintenance treatment for platinum sensitive, relapsed high grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer following a response to platinum-based chemotherapy. Secondary: To evaluate the safety and tolerability of rucaparib versus placebo in patients with platinum sensitive, relapsed high grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer as switch following a response to platinum-based chemotherapy.

II.C.2 Other studies in post-authorisation development plan
None