# Summary of the Risk Management Plan (RMP) for

# Rubraca® (Rucaparib)

RMP Summary: Version 2.2, dated 13 December 2018

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 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. In addition, Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy (see SmPC for the full indication). 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 | Myelosuppression<br>Nausea and vomiting |
| Important potential risks | MDS/AML<br>New primary malignancy<br>QTc interval prolongation<br>Photosensitivity<br>Embryotoxicity and teratogenicity<br>DDI with metformin, DDI with substrates of BCRP, e.g., rosuvastatin |
| Missing information | Use in patients for longer than 18 months<br>Effects of rucaparib on fertility<br>The effect on an infant of a nursing mother receiving rucaparib<br>Safety in patients with severe renal impairment<br>Safety in patients with moderate or severe hepatic impairment<br>Characterisation of metabolites of rucaparib<br>DDI with oral contraceptives<br>Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor |

***II.B Summary of important risks***

| **Important identified risk 1: Myelosuppression** | |
|---|---|
| Evidence for linking the risk to the medicine | Rucaparib can induce myelosuppression through effect on DNA repair and possible effect on division of bone marrow cells. Studies CO-338-010 and CO-338-017 showed that 43%, 8.0%, 1.4%, and 14.9% of the patients experienced anaemia, neutropenia, febrile neutropenia, and thrombocytopenia, respectively. Study CO-338-014 (ARIEL3) showed that overall, 36.3%, 12.6%, 1.3%, and 17.2% of the patients taking rucaparib experienced anaemia, neutropenia, febrile neutropenia, and thrombocytopenia, respectively compared to 5.3%, 1.6%, 0% and 1.1% overall in the placebo group. Myelosuppression is considered an important identified risk as severe myelosuppression can be a serious condition that if left untreated may lead to infections, hospitalisation, and even death. |
| Risk factors and risk groups | Many of the agents used in front- and later-line ovarian cancer therapies may cause permanent changes in the patient that alter tolerance profiles to future chemotherapeutic interventions.[37] For example, anaemia and leukopenia occur in more than half of patients with advanced ovarian cancer treated with cisplatin.[38] Between 1982 |

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| | and 1996, 547 patients with untreated advanced ovarian cancer entered the Gruppo Oncologico Nord-Ovest consecutive randomised trials, which included cisplatin-based chemotherapy. Myelotoxicity was one of the main toxicities observed, including leukopenia (52%), anaemia (51%), and thrombocytopenia (17%).[38]<br>Regression analysis has been used to demonstrate that carboplatin exposure and prior treatment are predictors of thrombocytopenia and leukopenia in patients with ovarian cancer.[39]<br>A systematic literature review of chemotherapy-induced neutropenia showed that older age (particularly > 65 years), previous chemotherapy or radiotherapy, female sex, pre-existing neutropenia or tumour involvement in the bone marrow, poor performance status, co-morbidities (eg, renal or liver dysfunction, and cardiovascular disease), and pre-existing conditions (eg, infection) are risk factors for developing severe chemotherapy-induced neutropenia.[40,41]<br>Clinical and experimental studies have suggested an age-related decline in the number of haematopoietic stem cells, as well as of the ability of the bone marrow to react to haematopoietic stress, such as haemorrhage or infection. Higher rates of myelosuppression are reported after chemotherapy in the elderly. Not only are neutropenic complications more frequent in the elderly, they are also often more severe, leading to higher rates of hospitalisation, longer hospital stays, and higher mortality, although, advanced age may also be associated with other patient characteristics that affect that risk.[42]<br>In a retrospective 2-year study of patients with a gynaecological cancer whose treatment regimen included carboplatin and paclitaxel, the effect of patient weight on haematological toxicity was analysed. Compared to the normal weight group (31 patients), the overweight group (21 patients, body mass index (BMI) $\geq$ 27 kg/m$^2$) showed a higher incidence of thrombocytopenia (95% CI, 1.51-27.72; $p < 0.02$) and anaemia (95% CI, 1.06-33.63; $p < 0.05$).[43] |
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*SmPC section: 4.2, 4.4, 4.8*<br>*PL section: 2, 4*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4)* |

| **Important identified risk 2: Nausea and vomiting** | |
|---|---|
| Evidence for linking the risk to the medicine | Pre-clinical and clinical trials showed GI toxicity with rucaparib treatment. Nausea/vomiting is considered an important identified risk as severe nausea and vomiting for a prolonged duration can be a serious condition that if left untreated may lead to further complications such as dehydration or hospitalisation. |
| Risk factors and risk groups | None were identified |
| Risk minimisation measures | **Routine risk minimisation measures**: |

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| | *SmPC section: 4.2, 4.4, 4.7, 4.8*<br>*PL section: 4*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4)* |

| **Important potential risk 1: MDS/AML** | |
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| 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).<br>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]<br>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]<br>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]<br>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]<br><br>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 |

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| | 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).<br>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 taxanecontaining regimens.<br>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**:<br>*SmPC section: 4.4, 4.8*<br>*PL section: 2*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4). After last dose of study drug, all patients will be monitored for MDS/AML until death, lost to follow up, withdrawal of consent or study closure.* |

| **Important potential risk 2: New primary malignancy** | |
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| 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**:<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Periodic review of collection and assessment of data emerging from the ongoing clinical programme and CO-338-043 (ARIEL4). After last dose of study drug, all patients will be monitored for new primary* |

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| | *malignancy until death, lost to follow up, withdrawal of consent or study closure.* |

| **Important potential risk 3: QTc interval prolongation** | |
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| 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**:<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |

| **Important potential risk 4: Photosensitivity** | |
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| Evidence for linking the risk to the medicine | Events of photosensitivity were reported in 11.0-21% of the patients taking rucaparib. Photosensitivity is considered an important potential risk as this may have a considerable impact on the patient's quality of life. |
| Risk factors and risk groups | Not applicable |
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*SmPC section: 4.4, 4.8*<br>*PL section: 2, 4*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4)* |

| **Important potential risk 5: Embryotoxicity and Teratogenicity** | |
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| 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**: |

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|---|---|
| | *SmPC section: 4.4, 5.3*<br>*PL section: 2*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |

| **Important potential risk 6: DDI with metformin, DDI with substrates of BCRP, e.g., rosuvastatin** | |
|---|---|
| Evidence for linking the risk to the medicine | Pre-clinical and clinical studies showed possible DDI with substrates of MATE1, MATE2-K, OCT1, OCT2, and BCRP. DDI can lead to toxicity especially in elderly population in which polypharmacy is common and hence it is an important potential risk. |
| Risk factors and risk groups | Genetic polymorphisms can significantly affect metabolism of drugs that are given concomitantly with rucaparib. |
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*SmPC section: 4.5,4.6, 5.2*<br>*PL section: 2*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Study CO-338-095 Arm A: A Phase 1, open label, DDI study to determine the effect of rucaparib on the PK of oral rosuvastatin in patients with advanced solid tumours* |

| **Missing information 1: Use in patients for longer than 18 months** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*SmPC section: 4.8*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4)* |

| **Missing information 2: Effect of rucaparib on fertility** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*SmPC section: 4.6, 5.3*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |

| **Missing information 3: The effect on an infant of a nursing mother receiving rucaparib** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**: |

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|---|---|
| | *SmPC section: 4.3, 4.6*<br>*PL section: 2*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |

| **Missing information 4: Safety in patients with severe renal impairment** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*SmPC section: 4.2, 5.2*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |

| **Missing information 5: Safety in patients with moderate or severe hepatic impairment** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*SmPC section: 4.2, 5.2*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Study CO-338-078: A Phase 1, open-label, parallel group study to determine the PK, safety and tolerability of rucaparib in patients with an advanced solid tumour and either moderate hepatic impairment or normal hepatic function* |

| **Missing information 6: Characterisation of metabolites of rucaparib** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |

| **Missing information 7: DDI with oral contraceptives** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**:<br>*SmPC section: 4.5*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*None* |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities**:<br>*Study CO-338-095 Arm B: A Phase 1, open label, DDI study to determine the effect of rucaparib on the PK of oral contraceptives in female patients with advanced solid tumours* |

| **Missing information 8: Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**: |

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|---|---|
| | *SmPC section: 5.1*<br>*Prescription only medicine*<br><br>**Additional risk minimisation measures**:<br>*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-338-043 (ARIEL4) | Primary: To compare the anti tumour efficacy, as measured by investigator assessment of the PFS, of oral single agent rucaparib, versus chemotherapy in patients with BRCA-mutant relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.<br>Secondary: To evaluate the safety and tolerability of rucaparib versus cytotoxic chemotherapy in patients with relapsed high grade serous or endometrioid tBRCA-mutant epithelial ovarian, fallopian tube, or primary peritoneal cancer. |
| 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.<br>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**

| Study name | Rationale and study objectives |
|---|---|
| Study CO-338-078 | A Phase 1, Open-Label, Parallel Group Study to Determine the PK, Safety and Tolerability of Rucaparib in Patients with an Advanced Solid Tumour and Either Moderate Hepatic Impairment or Normal Hepatic Function |
| Study CO-338-095 Arm B: In vivo DDI study with contraceptives | A phase 1, open label, DDI study to determine the effect of rucaparib on the PK of oral contraceptives in female patients with advanced solid tumours |
| Study CO-338-095 Arm A: In vivo DDI study with BCRP substrate | A phase 1, open label, DDI study to determine the effect of rucaparib on the PK of oral rosuvastatin in patients with advanced solid tumours |