GlaxoSmithKline AG

Swiss Summary of the Risk Management Plan (RMP) for Zejula (Niraparib)

RMP Summary:	Version 4, Juni 2023
EU RMP:	Version 7.0, 13.4.2023

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 minimize them.

The RMP summary of Zejula 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 Zejula in Switzerland is the „Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

GlaxoSmithKline AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP for Zejula.

Summary of risk management plan for Zejula (Niraparib)

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

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

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

I. The medicine and what it is used for

Zejula is authorised for monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy and as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy (see SmPC for the full indication). It contains Niraparib as the active substance and it is given by oral route.
Further information about the evaluation of Zejula's benefits can be found in Zejula's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004249/WC500239292.pdf

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

Important risks of Zejula, together with measures to minimise such risks and the proposed studies for learning more about Zejula'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) assessmentso that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Zejula 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 Zejula. 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	Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and sepsis) Hypertension MDS and AML
Important potential risks	SPM other than MDS and AML
Missing information	None

II.B Summary of important risks

Important identified risk: Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and sepsis)	
Evidence for linking the risk to the medicine	**Non-clinical**: Toxicology studies in rats and dogs showed haematologic adverse events, including decreased red cell mass, decreased leukocyte counts in the peripheral blood, decreased circulating platelets, and hypocellularity in the bone marrow. **Clinical**: In the NOVA study, 62.1%, 52% and 30.8% of the patients treated with niraparib experienced thrombocytopenia, anaemia and neutropenia events compared to 5%, 6.7%, and 6.1% in the placebo group, respectively. 11.2%, 4.1% and 1.4% of the thrombocytopenia, anaemia and neutropenia events were serious in the niraparib-treated patients compared to 0% in the placebo group. In the PRIMA study, 73%, 71.7% and 46% of the patients dosed with a fixed dose of 300 mg niraparib experienced thrombocytopenia, anaemia and neutropenia events, respectively; 53.8%, 50.3% and 35.5% of the patients dosed with individualised dose of niraparib experienced thrombocytopenia, anaemia and neutropenia events, compared to 4.9%, 17.6%, and 7.8% in the placebo group, respectively. 21.3%, 4.1% and 2.2% of the thrombocytopenia, anaemia and neutropenia events were serious in the fixed-dose of 300 mg niraparib-treated patients compared to 0% in the placebo group; 7.1%, 8.3% and 2.4% of the patients dosed with individualised dose of niraparib experienced thrombocytopenia,

	anaemia and neutropenia events compared to 0% in the placebo group. **Class-effect**: Haematological toxicities are known risks of other PARP inhibitors like olaparib and rucaparib. **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Cumulatively, up to DLP of 26 Mar 2021, a review of the haematological toxicities cases indicate that they are consistent with the known safety profile of niraparib.
Risk factors and risk groups	Thrombocytopenia: The incidence of on-treatment thrombocytopenia was more common among patients with lower baseline platelet counts (<150,000/µL) with 13 (93%) of 14 patients developing thrombocytopenia compared to those patients with higher baseline levels (<150,000/µL), although the incidence in this group was also high (211 of 352 patients, 60%). Patients with any prior history of thrombocytopenia also had a higher risk (121 of 172 patients, 70%) compared to those without a prior history (104 of 195 patients, 53%). There were no clinically meaningful differences in the overall incidence of any grade thrombocytopenia events based on age or number of prior platinum therapies. Thrombocytopenia events were more commonly reported in the niraparib arm among patients who were non-White (72%) compared to white patients (60%) and among patients with lower baseline weight (<67 kg; 67%) compared to those with higher weight (≥67 kg; 56%). Niraparib-treated patients who had a prior history of myelosuppression reported thrombocytopenia events at a higher incidence (64%) than those without a history of myelosuppression (50%). Thrombocytopenia events were also more common among niraparib-treated patients with ovarian cancer (62%) and fallopian tube cancer (67%) compared to those with primary peritoneal cancer (48%). The incidence of Grade 3/4 thrombocytopenia events was higher among niraparib-treated patients who received 2 prior platinum therapies (37%) compared to those who had received >2 prior therapies (26%) and among patients with lower baseline weight (<67 kg, 38%) compared to those with higher weight (≥67 kg, 28%). There was no effect of age, race, cancer subtype, or history of myelosuppression on the incidence of Grade 3/4 thrombocytopenia events. Thrombocytopenia events were more common in niraparib-treated patients who had a germline breast cancer gene mutation (g*BRCA*mut) (97 of 136 patients, 71%) compared to patients who did not (non-g*BRCA*mut; 128 of 231 patients, 55%). Analysis conducted by the Sponsor identified two clinical variables, body weight (<77 kg) and platelet count (<150,000/µL) associated with high-grade (i.e., grade 3-4 thrombocytopenia); patients with baseline body weight < 77 kg or baseline platelet count <150,000/µL platelets showed higher incidence of grade 3 or 4 thrombocytopenia during the first cycle of niraparib than patients with weight ≥77 kg and platelet count ≥150,000/µL. For patients who weigh less than 77 kg (170 lbs) or have baseline platelet count <150,000/µL, the recommended starting dose of ZEJULA is 200 mg (two 100 mg capsules or tablets) taken orally

	once daily. For all others, the recommended starting dose is 300 mg (three 100 mg capsules or tablets). If patients were monitored and managed by careful dose reduction, and in some cases transfusions, then the toxicity was generally reversible. The PRIMA study adopted the modified starting dose and this study safety analyses indicated that reducing the starting dose to 200 mg in these patients could reduce the incidence of grade 3 or 4 thrombocytopenia without compromising the efficacy of Zejula. Anaemia: The incidence of on-treatment anaemia was more common among patients with lower baseline haemoglobin concentration (<10 g/dL) with 18 (82%) of 22 patients developing anaemia compared to those patients with higher baseline levels (≥12 g/dL), although the incidence in this group was also high (63 of 154 patients, 41%). Patients with any prior history of anaemia also had a somewhat higher risk (126 of 236 patients, 53%) compared to those without a prior history (58 of 131 patients, 44%). There was no considerable difference in the incidence of anaemia events or Grade 3/4 anaemia events based on age, race, number of prior platinum therapies, or prior myelosuppression. Anaemia events were more common among niraparib-treated patients with lower baseline weight (<67 kg; 57%) compared to those with higher weight (≥67 kg; 43%) and in patients with ovarian cancer (52%) compared to those with fallopian tube cancer (41%) or primary peritoneal cancer (42%). The incidence of Grade 3 or 4 anaemia events was also higher among niraparib-treated patients with ovarian cancer (27%) compared to those with fallopian tube cancer (15%) or primary peritoneal cancer (16%). The incidence of Grade 3/4 anaemia events was higher among niraparib-treated patients in the g*BRCA*mut cohort (33%) compared to the non-g*BRCA*mut cohort (21%). Neutropenia: The incidence of on-treatment neutropenia was most common among patients with a prior history of Grade 4 neutropenia (20 of 36 patients, 56%) and was also more common among patients with any prior history of neutropenia (75 of 206 patients, 36%) compared to those without a prior history (36 of 161 patients, 22%). There was no considerable difference in the incidence of neutropenia events regardless of grade or for Grade 3/4 neutropenia events based on age, race, number of prior platinum therapies or cancer subtype. Patients with lower baseline weight (<67 kg) had a higher incidence of neutropenia events (38%) compared to those with higher weight (≥67 kg; 22%); similarly, patients who had a prior history of myelosuppression had a higher incidence (33%) compared to those without a history of myelosuppression (21%). The incidence of Grade 3/4 neutropenia events was higher in patients with lower baseline weight (24%) compared to those with higher weight (16%); the incidence of Grade 3/4 events was 21% for patients with a history of myelosuppression and 15% for those without a reported history. Overall, neutropenia events were reported at similar incidences among niraparib-treated patients in the g*BRCA*mut cohort (42 of 136 patients, 31%) compared to patients in the non-g*BRCA*mut

	cohort (69 of 231 patients, 30%). The incidence of Grade 3/4 neutropenia events was similar among niraparib-treated patients in the g*BRCA*mut cohort (21%) and in the non-g*BRCA*mut cohort (19%).
Risk minimisation measures	Routine risk minimisation measures: **SmPC sections** • Guidance in SmPC section 4.2 on dosing interruptions and adjustments in cases of haematological toxicity • Warning in SmPC section 4.4 that haematological toxicity is expected and to use caution with anticoagulation and antiplatelet drugs • Testing blood counts and monitoring is recommended in SmPC section 4.4 • Listed as adverse reactions in SmPC section 4.8 **PL Sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding low blood-cell counts. • Section 3 mentions that the recommended starting dose is 200 mg and if the patient weigh ≥ 77 kg and have platelet count ≥ 150,000/µL before starting treatment, the recommended starting dose is 300 mg. • Section 4 lists the haematologic side effects under the very common category. **Prescription status** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures: None

Important identified risk: Hypertension	
Evidence for linking the risk to the medicine	**Clinical**: In the NOVA study, 23.2% of the patients treated with niraparib experienced hypertension compared to 5.6% in the placebo group. There was only one serious event of hypertension in the niraparib group. In the PRIMA study, 18.7% of the patients dosed with a fixed dose of 300 mg niraparib experienced hypertension; 16.6% of the patients dosed with individualised dose of niraparib experienced hypertension, compared to 7% in the placebo group. There was only one serious event of hypertension in the fixed-dose niraparib group. **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Serial reviews of hypertension cases over time, up to DLP of 26 Mar 2021, indicate that they are consistent with the known safety profile of niraparib.
Risk factors and risk groups	There are multiple risk factors for hypertension in the general population including: Lifestyle factors (excess salt intake, excess

	body weight, smoking, alcohol), renal disease, endocrine disease, and family history. The incidence rates of TEAEs of hypertension regardless of grade and of Grade 3 hypertension were similar in patients <65 years and those ≥65 years who received niraparib. Patients in the niraparib arm who are White were more likely to have hypertension of any grade reported as a TEAE (21%) compared to non-Whites (11%); the incidence of Grade 3 hypertension was similar across race. Patients in the niraparib arm who had received more than 2 lines of prior platinum therapy were more likely to experience hypertension of any grade (26%) and Grade 3 hypertension (13%) compared to those who had received only 2 prior lines (16% and 6%, respectively). There were no substantial differences in the incidence of hypertension across cancer subtype.
Risk minimisation measures	Routine risk minimisation measures: **SmPC sections** • Warning in SmPC section 4.4 that hypertension has been reported with niraparib therapy and that blood pressure should be monitored • Listed as an adverse reaction in SmPC section 4.8 **PL sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding high blood pressure. • Section 4 lists high blood pressure under the very common category. **Prescription status** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures None
Important identified risk: MDS and AML	
Evidence for linking the risk to the medicine	**Clinical**: In the niraparib clinical development program up to the cut-off of 26 Mar 2021, the overall cumulative incidence of MDS/AML unadjusted for duration of follow-up, was comparable between the pooled niraparib treatment group and placebo group (1.0% vs. 0.9%). The total number of cases were, 23 in niraparib arm and 4 in placebo arm in GSK sponsored and unblinded clinical trials. However, in PR-30-5011-C NOVA study (median follow up time of 5.6 year) where patients with recurrent ovarian cancer were pre-exposed to 2 or more lines of platinum based chemotherapies, the subject incidence of MDS/AML was higher in niraparib arm (3.5%) than that in the placebo arm (1.7%). This finding is similar to the corresponding 3-year cumulative incidences of 3.5% and 2.1% of MDS/AML reported in published literature of a meta-analysis of randomized trials of PARPi. The event rate per patient follow-up year was 0.0117 and 0.0055, respectively. In g*BRCA*mut and non-

	g*BRCA*mut cohorts, the incidence of MDS/AML was 6.6% and 1.7% in patients receiving niraparib and 3.1% and 0.9% in patients receiving placebo, respectively. **Class-effect**: MDS and AML are known risks of other PARP inhibitors like olaparib and rucaparib [Olaparib SmPC; Rucaparib SmPC] **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Cumulatively, up to DLP of 26 Mar 2021, MDS/AML has been reported from the postmarketing setting from both spontaneous sources and postmarketing surveillance programs. Disproportional analyses showed relative higher reporting of MDS/AML associated with the use of niraparib in the GSK global safety database, FAERS database and EudraVigilance database. the post-marketing data has not provided support for this potential risk for niraparib.
Risk factors and risk groups	All clinical trial patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in g*BRCA*mut carriers. Some of the patients had a history of previous cancer or of bone marrow suppression. More general risk factors include the following: • Increased age. • Previous cancer therapy including radiotherapy, alkylating agents, epipodophyllotoxins, topoisomerase II inhibitors or colony-stimulating factors used to stimulate marrow function during chemotherapy [Hershman, 2007; Hijiya, 2009]. • Prolonged use of alkylator therapy for other illnesses – e.g., rheumatological disease. • Environmental toxins, especially benzene and other organic solvents, smoking, petroleum products, fertilisers, semi-metal, stone dusts and cereal dusts. Exposure to benzene can produce aplastic anaemia and pancytopenia, which can progress to AML. • Other genetically associated diseases – e.g., Schwachman-Diamond syndrome, Fanconi's anaemia and neurofibromatosis type 1 [ESMO Clinical Practice Guidelines, 2014]. • Antecedent haematological disorders including MDS predispose patients to AML [Catenacci, 2005]. • Genetic risk factors such as p53 or BRCA mutations
Risk minimisation measures	Routine risk minimisation measures: **SmPC Sections** • Warning in SmPC section 4.4 of the possible occurrence of MDS/AML and for treatment with niraparib to be discontinued if MDS/AML are confirmed • Listed as adverse reactions in SmPC section 4.8 **PL sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding MDS/AML.

	• Section 4 lists the MDS/AML side effects under the common category. **Prescription Status** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures None
Additional pharmacovigilance activities	• 3000-04-002 /GSK 214708: An integrated meta-analysis of MDS/AML and other SPM incidence in patients with ovarian cancer who have been treated with niraparib • 3000-04-001 /GSK 213705: PASS to evaluate the risks of MDS/AML and other second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (Niraparib)

Important potential risk: SPM other than MDS and AML	
Evidence for linking the risk to the medicine	**Clinical**: In the NOVA study, 5 patients treated with niraparib experienced SPM other than MDS and AML compared to one in the placebo group. In the PRIMA study there were 4 cases of malignancies other than MDS/AML in the fixed dose and none in the individualised dose compared to 3 cases in the placebo group. **Class-effect**: SPM other than MDS and AML are known risks of other PARP inhibitors like olaparib and rucaparib [Olaparib SmPC; Rucaparib SmPC]. **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Cumulatively, up to DLP of 26 Mar 2021, the post-marketing data has not provided support for this potential risk for niraparib.
Risk factors and risk groups	Prior DNA-damaging chemotherapeutic drugs represents a risk factor for development of new malignancies [Livraghi, 2015]. Curtis et al (2006) reported that excluding female genital sites, overall subsequent cancer risk was higher in blacks (O/E=1.42, excess absolute risk (EAR)=29) than whites (ratio of observed to expected cancers (O/E)=1.16, EAR=14). Women younger than age 50 years at ovarian cancer diagnosis, had a 58% increased risk of new malignancies, whereas risk declined to below unity among patients diagnosed at ages older than 70 years. Most of the overall excess was attributable to significantly increased risks for acute leukaemia, as well as for cancers of the breast, colon, rectum, small intestine, bladder, renal pelvis, eye, and intrahepatic bile ducts [Curtis, 2006]. The risk groups or risk factors for the MDS and AML are also applicable to the other SPM (see risk groups or risk factors for MDS and AML above).
Risk minimisation measures	Routine risk minimisation measures:

	Prescription Status • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures None
Additional pharmacovigilance activities	• 3000-04-002 /GSK 214708: An integrated meta-analysis of MDS/AML and other SPM incidence in patients with ovarian cancer who have been treated with niraparib • 3000-04-001; GSK 213705: PASS to evaluate the risks of MDS/AML and other second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (Niraparib)

II.C Post-authorisation development plan

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

The following study is a condition of the marketing authorization (PAES):

Study Short Name: PR-30-5017-C / GSK213359 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy

Purpose of the Study: The objectives are as follows:

Primary objective: To evaluate the efficacy of niraparib versus placebo as maintenance treatment, as measured by progression-free survival (PFS), in patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) with a complete response (CR) or partial response (PR) following front-line platinum-based chemotherapy treatment.

Secondary Objectives:
1. To evaluate additional measures of clinical benefit for niraparib versus placebo as maintenance treatment, such as overall survival (OS), patient-reported outcomes (PROs), time to first subsequent therapy (TFST), and time to progression on the next anticancer therapy (PFS2).
2. To evaluate the safety and tolerability of niraparib versus placebo

Exploratory Objectives:

1. To assess population pharmacokinetics (PK) and estimate PK parameters for niraparib and its major metabolite
2. To evaluate potential biomarkers related to ovarian cancer and poly(ADP-ribose) polymerase (PARP) inhibition (e.g. DNA repair pathways)
3. To explore the relationship between homologous recombination-deficient (HRD) status and platinum sensitivity in ovarian cancer patients who have initial response to front-line platinum therapy

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

Study Short Name: 3000-04-002 / GSK 214708: An integrated meta-analysis of MDS/AML and other SPM incidence in patients with ovarian cancer who have been treated with niraparib

Purpose of the Study:

- The primary endpoint is to compare the incidence rate of MDS/AML in patients with ovarian cancer treated with niraparib versus any other treatment comparator.

- The secondary endpoint is to compare the incidence rate of SPM in the same population.

- The third endpoint is to estimate incidence of MDS/AML and other SPM in patients with ovarian cancer treated with niraparib in pooled TESARO clinical studies.

Study Short Name: 3000-04-001 / GSK 213705: PASS to evaluate the risks of MDS/AML and SPM in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula® (Niraparib).

Purpose of the Study:

The objective of this PASS is to determine the risk of developing MDS/AML and SPM in patients administered niraparib in the routine clinical setting with:

- epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

or

– platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial to platinum-based chemotherapy

The objectives are as follows:

Primary: To estimate the incidence rate of MDS/AML, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients: 1) with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first line platinum-based chemotherapy or 2) with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy, treated with niraparib.

Secondary: To estimate the incidence rate of SPM, and the distribution of these events across different risk factors for SPM, in the same cohorts.

Exploratory: To compare the incidence rate ratios of MDS/AML and other SPM in niraparib-treated patients to a retrospective cohort of patients with similar disease and treatment characteristics, but who were not treated with any PARP inhibitor.

This summary was last updated in June 2023.