SWISS SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR ZEJULA®
(niraparib tosylate monohydrate)

TESARO Bio GmbH
RMP Summary: RMP Version 0.4 dated 11 September 2017
Summary of the Risk Management Plan (RMP) for ZEJULA®

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. TESARO Bio GmbH is fully responsible for the accuracy and correctness of the content of the here published summary RMP of ZEJULA.

Overview of the disease epidemiology

Zejula is indicated for the maintenance treatment of adult patients with high grade serous epithelial ovarian, fallopian tube, or primary peritoneal platinum sensitive relapsed cancer who are in response (complete or partial) to platinum-based chemotherapy.

Incidence and prevalence:
Ovarian cancer is the seventh most common cancer in women worldwide (18th most common cancer overall), with 239,000 new cases diagnosed in 2012 and around 152,000 deaths (Ferlay et al, 2015).

In the European Union (EU), ovarian cancer is the sixth most common cause of cancer death for females, and the 12th most common cause of cancer death overall.

In the United States (US), ovarian cancer is the fifth overall cause of cancer death in women and represents 5% of all cancer deaths (Siegel et al, 2014). Ovarian cancer is the deadliest of gynaecologic cancers. In 2016, it was estimated that there would be 22,280 new cases of ovarian cancer and an estimated 14,240 women would die of this disease in the US (SEER Stat Fact Sheets, 2016: Ovarian Cancer).

Ovarian cancer is the most common malignancy after breast cancer in women over 40 years of age, particularly in developed countries. Epithelial ovarian cancer occurs in about 90% of cases, and only 10% originate from germ cells, sex cords, or ovarian stroma cells. Approximately 75–80% of epithelial ovarian cases are of the serous histological type (Vargas, 2014).

Demographics of the population in the proposed indication (age, gender, racial and/or ethnic origin):
Ovarian cancer incidence is strongly related to age, with the highest incidence rates being in older females. Age-specific incidence rates rise sharply from around age 35-39, peak in those aged 80-84, and subsequently drop sharply. Age-standardised rates for White females with ovarian cancer range from 17.4 to 18.1 per 100,000. Rates for Asian females are significantly lower, ranging from 9.2 to 15.5 per 100,000 and the rates for Black females are also significantly lower, ranging from 6.6 to 12.1 per 100,000. (Cancer Research UK, 2016, www.cancerresearchuk.org).
Summary of treatment Benefits
The safety and efficacy of niraparib as maintenance therapy were established in a Phase 3 randomised, double-blind, placebo-controlled international trial (ENGOT-OV16 / NOVA) in patients with relapsed predominantly high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were platinum sensitive, defined by complete response (CR) or partial response (PR) for more than six months to their penultimate (next to last) platinum-based therapy.

Unknowns relating to treatment benefits
Unknowns and/or missing information regarding the safety of niraparib includes long-term use in patients with severe renal impairment and ESRD, and in patients with severe hepatic impairment (see section on summary of safety concerns).

Summary of safety concerns
Important risks of Zejula 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 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

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Haematological toxicity (thrombocytopenia, anaemia and neutropenia).</th>
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<td>Hypertension.</td>
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Important potential risks

- Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML).
- Second primary malignancies other than MDS and AML.
- Embryo-foetal toxicity
- Pneumonitis.

Missing information

- Exposure in patients with severe renal impairment and ESRD.
- Exposure in patients with severe hepatic impairment.

Summary of Important Identified Risks, Important Potential Risks and Missing Information

Important identified risk: Haematological toxicity

Evidence for linking the risk to the medicine

- NOVA CSR PR-30-5011-C
- http://patient.info/doctor/
- http://www.emedicinehealth.com/
- http://www.mayoclinic.org/diseases-conditions/

Risk factors and risk groups

- **Thrombocytopenia**: The incidence of on-treatment thrombocytopenia was more common among patients with lower baseline platelet counts (<125 x 10^9/L) with 13 (93%) of 14 patients developing thrombocytopenia compared to those patients with higher baseline levels (≥125 x 10^9/L), 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 gBRCA1mut (97 of 136 patients, 71%) compared to patients who did not (non-gBRCA1mut; 128 of 231 patients, 55%).
Anaemia: The incidence of on-treatment anaemia was more common among patients with lower baseline hemoglobin 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 gBRCAmut cohort (33%) compared to the non-gBRCAmut 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 gBRCAmut cohort (42 of 136 patients, 31%) compared to patients in the non-gBRCAmut cohort (69 of 231 patients, 30%). The incidence of Grade 3/4 neutropenia events was similar among niraparib-treated patients in the gBRCAmut cohort (21%) and in the non-gBRCAmut cohort (19%).

<table>
<thead>
<tr>
<th>Risk minimisation measures</th>
<th>Routine risk minimisation measures</th>
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<tbody>
<tr>
<td></td>
<td>Guidance in SmPC section 4.2 on dosing interruptions and adjustments in cases of haematological toxicity.</td>
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<tr>
<td></td>
<td>Warning in SmPC section 4.4 that haematological toxicity is expected and to use caution with anticoagulation and antiplatelet drugs.</td>
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<td></td>
<td>Testing blood counts and monitoring is recommended in section 4.4.</td>
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<td></td>
<td>Listed as adverse reactions in SmPC section 4.8.</td>
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<td></td>
<td>Prescription only medicine.</td>
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<td>Treatment under supervision of a specialist physician.</td>
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</table>

Additional risk minimisation measures
None
## Important identified risk: Hypertension

| Evidence for linking the risk to the medicine | NOVA CSR PR-30-5011-C  
|                                           | NICE guidelines [CG127], 2011  
|                                           | Law et al, 2003  
|                                           | [http://patient.info/doctor/hypertension](http://patient.info/doctor/hypertension)  
|                                           | [http://www.who.int/gho/ncd/risk_factors/blood_pressure_text/](http://www.who.int/gho/ncd/risk_factors/blood_pressure_text/)  

| 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  
|                           | - 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.  
|                           | - Prescription only medicine.  
|                           | - Treatment under supervision of a specialist physician.  

| Additional risk minimisation measures | None |
## Important potential risk: Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML)

### Evidence for linking the risk to the medicine
- BSCH Guidelines: MDS, 2013
- ESMO Clinical Practice Guidelines, 2014
- Aul, 1992
- Barzi & Sekeres, 2010
- Catenacci & Schiller, 2005
- Cogle, 2011
- Hershman et al, 2007
- Hijiya et al, 2009
- Morton, 2013
- Rollison, 2008

### Risk factors and risk groups
All 9 of the patients reporting MDS/AML had high-grade serous ovarian cancer; 4 of the 7 had gBRCAmut, 4 had non-gBRCAmut disease, and 1 patient had unknown BRCA mutation status. Eight of the 9 patients reported a prior history of myelosuppression with 7 of the 9 having received 3 or more prior lines of chemotherapy. 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 et al, 2007; Hijiya et al, 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, for example, 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 & Schiller, 2005).
- Genetic risk factors such as p53 or BRCA mutations.

### Risk minimisation measures
- **Routine risk minimisation measures**
  - Guidance in SmPC section 4.2 on dosing interruptions and adjustments in cases of haematological toxicity. 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.
  - Prescription only medicine.
  - Treatment under supervision of a specialist physician.

### Additional risk minimisation measure
- None

### Additional pharmacovigilance activities
- Meta-analysis of completed, ongoing and planned niraparib clinical studies for MDS/AML and other second primary malignancies.
- Risks of MDS/AML and Other Second Primary Malignancies in Adult Patients with Recurrent Epithelial Ovarian Cancer Receiving Maintenance Treatment with Zejula (Niraparib).
### Important potential risk: Second primary malignancies other than MDS and AML

**Evidence for linking the risk to the medicine**
CSR PR-30-5011-C. Non-Clinical studies.

**Risk factors and risk groups**
In a large US study, Curtis et al (2006) reported that excluding female genital sites, the overall subsequent cancer risk was higher in blacks (O/E=1.42, EAR=29) than whites (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.

The risk groups or risk factors for the MDS and AML are also applicable to the other second primary malignancies (see risk groups or risk factors for MDS and AML above).

**Risk minimisation measures**
Routine risk minimisation measures
- Prescription only medicine
- Treatment under supervision of a specialist physician

Additional risk minimisation measures
None

**Additional pharmacovigilance activities**
- Meta-analysis of completed, ongoing and planned niraparib clinical studies for MDS/AML and other second primary malignancies.
- Risks of MDS/AML and Other Second Primary Malignancies in Adult Patients with Recurrent Epithelial Ovarian Cancer Receiving Maintenance Treatment with Zejula (Niraparib).

### Important potential Risk: Embryofetal toxicity

**Evidence for linking the risk to the medicine**
Nonclinical studies and literature (Menissier de Murcia et al, 2003).

**Risk factors and risk groups**
Pregnancy.

**Risk minimisation measures**
Routine risk minimisation measures
- Warnings advise in SmPC section 4.4 and section 4.6 that women of childbearing potential should not become pregnant while on niraparib
- Prescription only medicine.
- Treatment under supervision of a specialist physician.

Additional risk minimisation measures
None

### Important potential Risk: Pneumonitis

**Evidence for linking the risk to the medicine**
CSR PR-30-5011-C

**Risk factors and risk groups**
Not identified in the target patient population.

**Risk minimisation measures**
Routine risk minimisation measures
- Prescription only medicine
- Treatment under supervision of a specialist physician

Additional risk minimisation measures
None
<table>
<thead>
<tr>
<th>Missing information: Patients with severe renal impairment and ESRD</th>
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<td><strong>Risk minimisation measures</strong></td>
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<th>Missing information: Patients with severe hepatic impairment</th>
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<tr>
<td><strong>Risk minimisation measures</strong></td>
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<td>- Warning in SmPC section 4.2 that there is no data on the effect of niraparib in patients with severe hepatic impairment and should be used with caution.</td>
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</table>

**List of Studies in the post authorization plan**
The following safety studies are listed in the post-authorization plan:

1. Meta-analysis of completed, ongoing and planned niraparib clinical studies for MDS/AML and other second primary malignancies.
2. Risks of MDS/AML and other second primary malignancies in adult patients with recurrent epithelial ovarian cancer receiving maintenance treatment with niraparib.

**Studies that are a condition of Swiss marketing authorization**
The studies that are a condition of the Swiss marketing authorization are summarized below:

2. Submit PSUR/PBRER according to guidelines.
5. Submit Final Report for PK study in patients with advanced solid tumors with either normal hepatic function or moderate hepatic impairment (PMR 3187) by 01.08.2019.

**Summary of RMP changes overtime**
Not applicable as the Summary of Risk Management Plan is consistent with Swissmedic approved niraparib RMP Version 0.4 dated 11 September 2017.