

**Summary of the Risk Management Plan (RMP) for
Lynparza[®] (Olaparib)**

50 mg, capsules
100 mg and 150 mg, film-coated tablets

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

1 THE MEDICINE AND WHAT IT IS USED FOR

Olaparib is a PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitor. PARP inhibitors destroy cancer cells by exploiting deficiencies in DNA pathways. These specific cancer cells can be identified by response to platinum chemotherapy or by looking for faulty (mutated) DNA repair genes, such as *BRCA* (BRCAst CAncer) genes.

Olaparib capsule and tablet formulations are authorised, as monotherapy, for the maintenance treatment of *BRCA*-mutated relapsed ovarian, cancer, once the cancer has responded to platinum-based chemotherapy.

Olaparib tablet formulation is used, as monotherapy, for the maintenance treatment of adult patients with newly diagnosed advanced *BRCA*-mutated ovarian cancer, who are in response to first-line platinum-based chemotherapy.

Olaparib tablet formulation is also authorised as monotherapy for the treatment of adult patients with germline *BRCAm* HER2-negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting (see SmPC for the full indications). Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy (see SmPC for the full indications).

Olaparib tablet formulation is also used as monotherapy for the adjuvant treatment of adult patients with *BRCA*1/2-mutations (germline) who have HER2-negative high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy.

Olaparib tablet is also used as monotherapy for treatment of a type of pancreatic cancer (*BRCA* mutated), that has responded to the first treatment with standard platinum-based chemotherapy. A test is used to find out whether you have *BRCA*-mutated pancreatic cancer.

Olaparib tablet is also authorised to be used in combination with bevacizumab for the maintenance treatment of patients with advanced (FIGO stages III and IV) high-grade serous ovarian cancer following first-line platinum-taxane chemotherapy with bevacizumab who are in complete or partial response and whose ovarian carcinoma is associated with a *BRCA* mutation and/or another homologous recombination deficiency (HRD) with genomic instability.

Olaparib tablet is also authorised to be used as monotherapy for the treatment of adult patients with *BRCA*-mutated (germline and/or somatic) metastatic castration-resistant prostate cancer who have progressed following a prior new hormonal agent (see SmPC for the full indications).

The capsule and tablet formulations contain olaparib as the active substance and are given by oral administration.

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of olaparib, together with measures to minimise such risks and the proposed studies for learning more about olaparib'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 (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of olaparib, these measures are supplemented with additional risk minimisation measures mentioned under the relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed 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 olaparib is not yet available, it is listed under 'missing information' below.

2.1. List of important risks and missing information

Important risks of olaparib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 olaparib. 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 (eg, on the long term use of the medicine).

Table 1 List of important risks and missing information

Important identified risks	Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)
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Table 1 List of important risks and missing information

Important potential risks	New primary malignancies Effects on embryofetal survival and abnormal development
Missing information	Long term exposure to/potential toxicity to olaparib

2.2. Summary of important risks

Table 2 Important identified risks

MDS/AML	
Evidence for linking the risk to the medicine	Case reports of MDS/AML have been received from clinical studies and through spontaneous reporting.
Risk factors and risk groups	<p>Risk factors include prior treatment with cytotoxic chemotherapy and/or irradiation, occupational exposure, and smoking (Strom et al 2008). Secondary MDS occurs as a late toxicity of cancer treatment, usually with a combination of radiation and the radiomimetic alkylating agents such as bisulfan or procarbazine (with a latent period of 5 to 7 years) or the DNA topoisomerase inhibitors (2 years). Both acquired aplastic anaemia following immunosuppressive treatment and genetic Fanconi anaemia can evolve into MDS. Patients with Fanconi anaemia have a higher risk of MDS and AML (Kutler et al 2003). There is some evidence that the risk of MDS/AML may be increased in patients with BRCA mutation (Friedenson 2007; Cole and Strair 2010), but there is not sufficient published data to quantify this risk due to the rarity of the event and historical lack of routine BRCA mutation screening. Germline BRCA mutation is known to predispose patients to the development of solid tumours, notably ovarian and breast tumours and Cole and Strair have hypothesised that a deficiency in the expression of BRCA genes may also render patients more vulnerable to the adverse effects of chemotherapy and therefore put them at an increased risk of MDS/AML (Cole and Strair 2010). Recently, Bolton et al investigated the relationship between clonal haematopoiesis and PARP inhibitor therapy and found that patients exposed to PARP inhibitor therapy were more likely to have clonal haematopoiesis (33%), particularly those in the DNA damage response pathway compared to those exposed to other systemic therapies or radiation (18%), or untreated patients (16%) (Bolton et al 2020).</p> <p>Overall in monotherapy and combination studies (N= 7161), there were 2594 (41.3 %) patients with <i>gBRCA1</i> mutation of whom 40/2954 (1.4 %) had MDS/AML and 1516 (21.2 %) patients with <i>gBRCA2</i> mutation of whom 14/ 1516 (0.9 %) had MDS/AML.</p>

Table 2 Important identified risks

Risk minimisation measures	Routine risk communication in: <ul style="list-style-type: none">• SmPC Section "Warnings and precautions"• Patient leaflet Section "When is caution necessary when taking Lynparza?" and "What side effects may Lynparza have?"
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none">• Follow-up targeted safety questionnaire• Cumulative assessment (provided within each annual periodic benefit risk evaluation report)

Table 3 Important potential risks

New primary malignancies	
Evidence for linking the risk to the medicine	Case reports of new primary malignancies (NPMs) have been received from clinical studies and post-marketing use.

Table 3 Important potential risks

<p>Risk factors and risk groups</p>	<p>Patients with ovarian cancer, breast cancer and BRCA mutations are at risk of developing other common cancers (Bergfeldt et al 1995; Fowble et al 2001; Wesolowski et al 2007). Therapy induced risk factors, including previous radiotherapy or chemotherapy with DNA damaging agents, are known to increase the incidence of malignant disease (eg, bladder cancer, lymphoma and leukaemia).</p> <p>Other common risk factors include:</p> <ul style="list-style-type: none"> • Exposure to ultraviolet-light which can induce DNA damage, causing skin cancer • Exposure to environmental factors eg, formaldehyde, asbestos • Dietary factors in cancer of colon and breast • Hormonal factors eg. oestrogen dependent (endometrial and breast cancers) • Smoking, which has been connected to several types of cancer eg. lung • Immunological factors: some cancer patients have depressed immunological function and certain states of immunosuppression can predispose for specific malignant disease. <p>Overall in monotherapy and combination studies (N= 7161), there were 2954 (41.3 %) patients with <i>gBRCA1</i> mutation of whom 75/2954 (2.5 %) had NPM and 1516 (21.2 %) patients with <i>gBRCA2</i> mutation of whom 25/1516 (1.6 %) had NPM.</p>
<p>Risk minimisation measures</p>	<p>There are no routine risk minimisation activities for new primary malignancy.</p>
<p>Additional pharmacovigilance activities</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> • Follow-up targeted safety questionnaire
<p>Effects on embryofoetal survival and abnormal development</p>	

Table 3 **Important potential risks**

Evidence for linking the risk to the medicine	Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg bd. Olaparib was not mutagenic in a bacterial mutation test (Ames), but was clastogenic in a chromosome aberration test in vitro and induced micronuclei in the bone marrow of rats following oral dosing.
Risk factors and risk groups	Not known.
Risk minimisation measures	Routine risk communication in: <ul style="list-style-type: none">• SmPC Sections "Warnings and precautions" and "Pregnancy, lactation"• Patient leaflet Section "When should Lynparza not be taken?" and "Can Lynparza be taken during pregnancy or when breastfeeding?"

Table 4 Missing information

Long-term exposure to/potential toxicity to OLAPARIB	
Risk minimisation measures	None
Additional pharmacovigilance activities	None

3 POST-AUTHORISATION DEVELOPMENT PLAN

3.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study D0818C00001 (SOLO1): A study of the safety and effectiveness of olaparib tablets in women with advanced ovarian cancer with certain changes in their *BRCA1* or *BRCA2* genes (mutations), whose cancer has responded (reduced in size or disappeared) to first line platinum chemotherapy.

Purpose of the study: To investigate the efficacy of olaparib tablets by PFS (using investigator assessment of scans according to modified RECIST 1.1) as maintenance monotherapy in *BRCA* mutated advanced ovarian cancer patients who achieved complete or partial response following first line platinum-based chemotherapy.

Study D081SC00001 (PROpel): A study of the safety and efficacy of Lynparza tablets in men with mCRPC in combination with abiraterone (an androgen receptor signalling inhibitor) and prednisone or prednisolone.

Purpose of the study: To investigate the efficacy of Lynparza tablets by rPFS as combination therapy with abiraterone and prednisone or prednisolone in mCRPC who have not received prior chemotherapy or new hormonal agents (NHAs) for mCRPC.

3.2 Other studies in post-authorisation development plan

There are no studies required for olaparib.