Summary of the Risk Management Plan (RMP) for

Lynparza® (Olaparib)

50 mg, capsules
100 mg and 150 mg, filmcoated 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 Lynparza 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 Lynparza 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 Lynparza.
1. THE MEDICINE AND WHAT IT IS USED FOR

LYNPARZA capsule formulation is authorised, as monotherapy, for the maintenance treatment of adult patients with platinum sensitive relapsed breast cancer susceptibility gene (BRCA)-mutated (BRCAm) (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (complete response or partial response) to platinum-based chemotherapy.

LYNPARZA tablet formulation is authorised, as monotherapy, for the maintenance treatment of patients with newly diagnosed advanced (FIGO stages III and IV) BRCA1/2-mutated germline and/or somatic ovarian cancer.

LYNPARZA tablet formulation is authorised, as 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.

LYNPARZA tablet formulation is also authorised as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. 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).

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 LYNPARZA, together with measures to minimise such risks and the proposed studies for learning more about LYNPARZA’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 LYNPARZA, 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 LYNPARZA is not yet available, it is listed under ‘missing information’ below.

2.1. List of important risks and missing information

Important risks of LYNPARZA 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 LYNPARZA. 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

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important potential risks</td>
<td>Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)</td>
</tr>
<tr>
<td></td>
<td>New primary malignancies</td>
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<tr>
<td></td>
<td>Pneumonitis</td>
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<td></td>
<td>Medication errors associated with dual availability of capsules and tablets</td>
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<tr>
<td></td>
<td>Effects on embryofoetal survival and abnormal development</td>
</tr>
<tr>
<td>Missing information</td>
<td>Long term exposure to/potential toxicity to LYNPARZA</td>
</tr>
</tbody>
</table>
2.2. **Summary of important risks**

There are no important identified risks for LYNPARZA.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Important potential risks</th>
</tr>
</thead>
</table>

<p>| 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 | 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). Overall in monotherapy and combination studies (N=2298), there were 990 (43.1%) patients with ( gBRCA1 ) mutation of whom 15/990 (1.5%) had MDS/AML and 455 (19.8%) patients with ( gBRCA2 ) mutation of whom 7/455 (1.5%) had MDS/AML. |
| Risk minimisation measures | Routine risk communication in: |
| | • SmPC Section 4.4 |
| | • PL Section 2 |
| | Routine risk minimisation activities recommending specific clinical measures to address the risk: |
| | <strong>SmPC Section 4.4</strong>: Guidance is provided for monitoring and management. |
| | <strong>PL Section 2</strong>: Advice regarding low blood counts and the signs and symptoms to look out for. |
| Additional pharmacovigilance activities | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: |
| | • Follow-up targeted safety questionnaire |
| | • Cumulative review (provided concurrent with each annual periodic benefit risk evaluation report) |</p>
<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Case reports of new primary malignancies (NPMs) have been received from clinical studies and post-marketing use.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>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). Other common risk factors include:</td>
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<tr>
<td></td>
<td>• Exposure to ultraviolet-light which can induced DNA damage, causing skin cancer</td>
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<td></td>
<td>• Exposure to environmental factors eg, formaldehyde, asbestos</td>
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<tr>
<td></td>
<td>• Dietary factors in cancer of colon and breast</td>
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<td></td>
<td>• Hormonal factors eg, oestrogen dependent (endometrial and breast cancers)</td>
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<td></td>
<td>• Smoking, which has been connected to several types of cancer eg, lung</td>
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<td></td>
<td>• Immunological factors: some cancer patients have depressed immunological function and certain states of immunosuppression can predispose for specific malignant disease.</td>
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<tr>
<td>Overall in monotherapy and combination studies (N=2298), there were 990 (43.1%) patients with gBRCA1 mutation of whom 14/990 (1.4%) had NPM and 455 (19.8%) patients with gBRCA2 mutation of whom 9/455 (2%) had NPM.</td>
<td></td>
</tr>
<tr>
<td>Risk minimisation measures</td>
<td>There are no routine risk minimisation activities for new primary malignancy.</td>
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<tr>
<td>Additional pharmacovigilance activities</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</td>
</tr>
<tr>
<td></td>
<td>• Follow-up targeted safety questionnaire</td>
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</table>

**New primary malignancies**

**Pneumonitis**

| Evidence for linking the risk to the medicine | Detailed case reports of pneumonitis have been received from clinical studies and post marketing use. |
## Risk factors and risk groups

Patients with lung disorders including cancer (lung and breast), lung metastases, medical history of medications/chemotherapy (including alkylating agents), radiation treatment, occupational and environmental factors are associated with the development of interstitial lung disease (ILD). Risk of acute alveolar damage due to infection may be increased in patients with previous chemotherapy and myelosuppression.

## Risk minimisation measures

Routine risk communication in:

- SmPC Section 4.4
- PL Section 2

Routine risk minimisation activities recommending specific clinical measures to address the risk:

**SmPC Section 4.4:** Guidance is provided for monitoring and management

**PL Section 2:** Advice on the signs and symptoms of possible pneumonitis.

## Additional pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Follow-up targeted safety questionnaire

## Medication errors associated with dual availability of capsules and tablets

### Evidence for linking the risk to the medicine

Underdosing of LYNPARZA has the potential for lack of efficacy; overdosing of LYNPARZA could result in an exacerbation of ADRs.

### Risk factors and risk groups

During the period when both formulations are on the market there is a risk of overdose or underdose due to potential confusion between the differences in posology for the 2 formulations by either the prescriber, dispenser or patient.
### Risk minimisation measures

Routine risk communication in:
- SmPC Section 4.2
- PL Section 3

Routine risk minimisation activities recommending specific clinical measures to address the risk:

**SmPC Section 4.2:** Statement informing that LYNPARZA is available as tablets and capsules which are not to be used interchangeably due to differences in the dosing and bioavailability of each formulation.

**PL Section 3:** Statement informing that LYNPARZA is available as tablets and capsules which are not the same and not to be used interchangeably.

**Additional risk minimisation measures:**
Distribution of a Direct healthcare Professional Communication (DHPC) to prescribers and pharmacists providing clear information on the 2 formulations.

### Effects on embryofoetal survival and abnormal development

**Evidence for linking the risk to the medicine**

Nonclinical studies in rats have shown that LYNPARZA causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg bd. LYNPARZA 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:
- SmPC Sections 4.4, 4.6
- PL Section 2

Routine risk minimisation activities recommending specific clinical measures to address the risk:

**SmPC Section 4.4, 4.6:** Advice on contraception and pregnancy.

**PL Section 2:** Advice on contraception and pregnancy.
Table 3  Missing information

<table>
<thead>
<tr>
<th>Long-term exposure to/potential toxicity to LYNPARZA</th>
</tr>
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<tbody>
<tr>
<td>Risk minimisation measures</td>
</tr>
<tr>
<td>Additional pharmacovigilance activities</td>
</tr>
</tbody>
</table>

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 D0816C00002 (SOLO2):** A study of the safety and effectiveness of LYNPARZA tablets in the treatment of women with ovarian cancer who have certain changes in their BRCA1 or BRCA2 genes (mutations)

Purpose of the study: To investigate the safety and effectiveness of LYNPARZA in women with advanced ovarian cancer patients who have BRCA1 or BRCA2 mutations, who have had at least 2 courses of treatment with platinum-based chemotherapy and whose cancer has responded (reduced in size or disappeared) to the most recent course of chemotherapy.

**Study D0816C00012 (ORZORA):** A study of the safety and effectiveness of LYNPARZA tablets in the treatment of women with ovarian cancer who have certain changes in their BRCA1 or BRCA2 genes (mutations) detected in the tumour but absent from blood testing.

Purpose of the study: To investigate the safety and effectiveness of LYNPARZA tablet in women with ovarian cancer who have previously responded to platinum based chemotherapy. Patients will be enrolled who carry a BRCA mutation detected in tumour but absent from blood testing.

**Study D0816C00020 (OPINION):** A study of the safety and effectiveness of LYNPARZA in the treatment of women with ovarian cancer that is sensitive to platinum chemotherapy and who do not have germline BRCA1/2 mutations.

Purpose of the study: To determine the efficacy by progression-free survival (PFS) (investigator-recorded assessments according to modified Response Evaluation Criteria In Solid Tumours of LYNPARZA maintenance monotherapy in non-germline BRCA mutated (gBRCAm) PSR ovarian cancer.

**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.

3.2 Other studies in post-authorisation development plan

There are no studies required for LYNPARZA.
LIST OF REFERENCES

Antoniou et al 2003

Bartsch et al 2009

Bergfeldt et al 1995

Bray et al 2013

Cancer Research UK

Cardoso et al 2017

Cole and Strair 2010

Coleman et al 2015
Colombo et al 2010

Colzani et al, 2014

Eccles et al 2016

Evans et al 2011

Ferlay et al 2013a

Ferlay et al 2013b

Fowble et al 2001

Friedenson 2007
Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer 2007;7:152.

Globocan 2012

Harter et al 2017
Hennessy et al 2010

Hirsch-Yechezkel et al 2003

Høberg-Vetti et al 2016

Horner et al 2009

Howlader et al 2014

Key et al 2001

Kutler et al 2003

Ledermann et al 2013

Leone et al 1999

Lowe et al 2013
Luporsi et al 2013

Marschner et al 2013

Leone et al 1999

Lowe et al 2013

Luporsi et al 2013

Marschner et al 2013

Moreno-Aspitia and Perez 2009

NCCN 2017

NCCN Ovarian 2018

Oonk et al 2012
Pang et al 2013

Purushotham et al 2014

Robertson et al 2012

Sant et al 2003

Sant et al 2015

Savci-Heijink et al 2015

Siegel et al 2018

Strom et al 2008

Travis et al 1999

van den Broek et al 2015
Walter et al 2012

Weiderpass and Labreche 2012

Wesolowski et al 2007

Will et al 2012

Winter et al 2016

Woll et al 2014