SUMMARY OF THE RISK MANAGEMENT PLAN FOR LYNPARZA (OLAPARIB)

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

Lynparza's SmPC and its PL give essential information to healthcare professionals and patients on how Lynparza should be used.

This summary of the RMP for Lynparza 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 EPAR.

Important new concerns or changes to the current ones will be included in updates of Lynparza's RMP.

I: THE MEDICINE AND WHAT IT IS USED FOR

Lynparza 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* (BReast CAncer) genes.

Lynparza is authorised, as monotherapy, for the maintenance treatment of *BRCA*-mutated relapsed ovarian, cancer, once the cancer has responded to platinum-based chemotherapy, and 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.

Lynparza 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 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).

Lynparza is also used as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2*-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

Lynparza 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.

Lynparza is also used as monotherapy for treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA1/2* mutations (germline and/or somatic) who have progressed following prior therapy that included new hormonal agent.

Lynparza in combination with bevacizumab is used for the maintenance treatment of adult patients with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) following completion of first-line platinum-based chemotherapy with bevacizumab and whose cancer is associated with HRD positive status defined by either a *BRCA1/2* mutation and/or genomic instability.

The tablets contain Lynparza as the active substance and are given by oral administration.

Further information about the evaluation of Lynparza's benefits can be found in Lynparza's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/003726/human_med_001831.jsp.

II: 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, including PBRER 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 Lynparza is not yet available, it is listed under 'missing information' below.

II: 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 II-1 List of Important Risks and Missing Information

Important identified risks	Myelodysplastic syndrome/Acute myeloid leukaemia
Important potential risks	New primary malignancies Effects on embryofoetal survival and abnormal development
Missing information	Long term exposure to/potential toxicity to olaparib

II: 1.1 Summary of Important Risks

Table II-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	Risk factors include prior treatment with cytotoxic chemotherapy and/or irradiation, occupational exposure, and smoking (Strom et al 2009). 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).

Table II-2 Important Identified Risks

MDS/AML	
	Overall in monotherapy and combination studies (N=7161), there were 2594 (41.3%) patients with *gBRCA1* mutation of whom 40/2954 (1.4%) had MDS/AML and 1516 (21.2%) patients with *gBRCA2* mutation of whom 14/1516 (0.9%) had MDS/AML.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4
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)

Table II-3 Important Potential Risks

New primary malignancies	
Evidence for linking the risk to the medicine	Case reports of NPMs have been received from clinical studies and post-marketing use.
Risk factors and risk groups	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: • Exposure to ultraviolet-light which can induced 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. Overall in monotherapy and combination studies (N=7161), there were 2954 (41.3%) patients with *gBRCA1* mutation of whom 75/2954 (2.5%) had NPM and 1516 (21.2%) patients with *gBRCA2* mutation of whom 25/1516 (1.6%) had NPM.
Risk minimisation measures	There are no routine risk minimisation activities for new primary malignancy.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire

Table II-3 Important Potential Risks

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 minimisation measures: • SmPC Sections 4.4, 4.6 • PL Section 2

Table II-4 Missing Information

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

III: POST-AUTHORISATION DEVELOPMENT PLAN

III: 1 STUDIES WHICH ARE CONDITIONS OF THE MARKETING AUTHORISATION

The following study is a condition of the marketing authorisation:

Study D0818C00001 (SOLO1): A study of the safety and efficacy of Lynparza 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 Lynparza 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.

III: 2 OTHER STUDIES IN POST-AUTHORISATION DEVELOPMENT PLAN

There are no studies required for Lynparza.