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Summary of the risk management plan (RMP) for Lynparza (olaparib)

This is a summary of the risk management plan (RMP) for Lynparza, which details the measures to be taken in order to ensure that Lynparza is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Lynparza, which can be found on Lynparza's EPAR page.

Overview of disease epidemiology

Lynparza (olaparib) is a cancer medicine that is used to treat adult women with cancer of the ovaries, including cancer of the peritoneum (the lining of the inside of the abdomen) or fallopian tubes, who have mutations (defects) in their *BRCA*1 or *BRCA*2 genes and whose tumours are responding to treatment with platinum chemotherapy.

Ovarian cancer is the fifth most common newly diagnosed cancer in women in Europe (44,150 new cases during 2012). Most women are aged 55 to 64 years old when they are diagnosed. The risk of getting ovarian cancer is increased in women who have had few or no children, in women who started menstruation early and in women who had a late menopause. There is also a greater risk if family members have had the disease.

Ovarian cancer is difficult to detect in its early stages, and three quarters of patients have advanced disease when they are diagnosed. Chemotherapy can halt or delay tumour growth, but the cancer almost always returns. Survival rates are improving, but historical data has shown only 1 in 5 women are alive 5 years after diagnosis.

Summary of treatment benefits

Lynparza has been shown to increase the time patients live without their disease getting worse in one main study involving 265 patients. Patients in the study had high grade serous ovarian cancers, including fallopian tube or peritoneal. Patients had undergone treatment with two or more regimens of platinum-based chemotherapy, and they had had a durable response (the cancer had not progressed for at least 6 months) before the last regimen. This response to platinum medicines justified the use of the last platinum-based treatment. Lynparza was given not later than 8 weeks after the last cycle of platinum-based medicines, when the tumour was diminishing in size or had completely disappeared. Around half of the patients in the study had *BRCA* mutations. These mutations were, in most cases, hereditary.

Patients who had a *BRCA* mutation and were treated with Lynparza lived on average significantly longer without their disease getting worse than patients who had a *BRCA* mutation and were treated with placebo (a dummy treatment): 11.2 months versus 4.3 months, respectively.

Unknowns relating to treatment benefits

Most patients treated with Lynparza in the clinical studies were white Caucasians. Very few patients studied had liver or kidney problems, so the safety and effectiveness of Lynparza in such patients is unknown.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Effects on the blood (haematological toxicity)	Patients treated with Lynparza have experienced anaemia (reduction in red blood cell count or haemoglobin), reductions in the numbers of white blood cells and reductions in numbers of platelets (components that help the blood to clot): • Anaemia occurred in approximately 4 out of 10 patients • A reduction in white blood cell count occurred in less than 2 out of 10 patients • A reduction in platelet count occurred in less than 1 out of 20 patients Most of the effects on blood cell counts in the Lynparza clinical studies were mild to moderate, and most did not cause any symptoms in patients. However, anaemia may cause tiredness, shortness of breath, pale skin or fast heart beat; reductions in white cell count can lead to increased risk of fever or greater risk of infection; and reductions in platelet count may lead to an increased risk of a bruising or bleeding for longer if injured.	These effects can be managed making sure blood counts are satisfactory before starting treatment and by monitoring with regular blood testing of patients whilst taking treatment with Lynparza, (at least once per month for the first year of treatment and as needed after that). Any effects on the blood should be treated as necessary, by either reducing the dose of Lynparza, or by briefly interrupting treatment. Severe effects on the blood may need to be treated by giving medication or transfusions. If the results of blood tests have not returned to normal after a 4-week interruption in treatment, testing of the bone marrow is recommended.
Raised creatinine levels	Patients treated with Lynparza have experienced increases in creatinine in their blood. Creatinine is a measurement of the function of the kidneys. The increase in creatinine observed was generally mild or moderate and kidney function was not affected.	
Feeling sick (nausea) and being sick (vomiting)	Side effects were generally mild or moderate and did not require any change in treatment. Approximately two thirds of patients treated with Lynparza reported nausea. Mild to moderate nausea can lead to loss of appetite or an	These effects can be managed by the use of anti-sickness medications.

Risk	What is known	Preventability
	involuntary urge to be sick. Approximately 4 out of 10 patients treated with Lynparza reported being sick. Some patients were treated with anti-sickness medicines.	

Important potential risks

Risk	What is known
Bone marrow abnormalities and cancers (myelodysplastic syndrome/acute myeloid leukaemia)	Myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) have been reported in a small number of patients who have taken olaparib alone or in combination with other cancer medicines. The majority of these cases have been fatal. The majority of patients had a BRCA mutation (a defect in one of the two BRCA genes) and some had a history of previous cancer or of bone marrow abnormalities. These patients had received extensive previous chemotherapy, which might have contributed to causing these symptoms. MDS is a pre-cancerous abnormality of the bone marrow. Symptoms include weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness and blood in urine or stools. MDS can progress to AML, which is a cancer of the blood and bone marrow where the cells produced by the bone marrow are abnormal, resulting in anaemia, infection, or easy bleeding. Both MDS and AML are serious conditions, which can result in death. Less than 1 in 100 olaparib-treated patients developed either MDS or AML. A similar number of placebo or chemotherapy-treated patients also developed MDS or AML.
Inflammation of the lungs (pneumonitis)	One in 200 patients treated with Lynparza reported pneumonitis. A similar number of placebo- or chemotherapy- treated patients also developed pneumonitis. Patients with pneumonitis may have difficulty breathing, and may experience coughing and wheezing which affects their quality of life. Pneumonitis is a serious condition that often requires hospitalisation. If spotted early, however, there is a better chance that it can be successfully treated.
Development of new types of cancers (other than bone marrow cancers)	The number of Lynparza-treated patients in the clinical trial programme who reported a new type of cancer, other than bone marrow cancers, was small (less than 1 in 100 patients), similar to the number of placebo-treated patients. The rate of development of new types of cancers in Lynparza-treated patients was similar to that reported in the medical literature on ovarian and breast-cancer patients. Due to the way that Lynparza works in the body, patients may potentially be at an increased risk of developing new cancers, although there may also be other reasons, e.g., previous treatment with chemotherapy, family history, environmental risks etc.
Use in a way that is different from that described in the approved prescribing information ('off-	The authorised use of Lynparza is described in the summary of product characteristics (SmPC) and package leaflet (PL). The use of Lynparza in ways that are different to that described in the SmPC is called 'off-label' use. Off-label use may include: use in children, use in combination with chemotherapy medicines, use in the treatment of other types of cancer, and use in the

Risk	What is known
label' use)	treatment of diseases other than cancer. Off-label use of Lynparza is a potential risk to patients, as its safety and effectiveness is unknown. Some of the likely risks of off-label use for Lynparza can be predicted, based on information from other clinical studies with Lynparza. These studies show that using Lynparza together with other chemotherapy medicines can lead to increased effects on the blood resulting in reduction in the numbers of white blood cells and platelets, and anaemia. The potential effectiveness of Lynparza treatment for other cancers or diseases, or in other types of patients, is likely to be unknown.
Potential for medication errors	Patients who take the recommended dose of Lynparza have to take 8 capsules (400 mg) twice a day (a total of 16 capsules each day taken as two separate doses). This high number of capsules could possibly lead to medication errors especially if patients take several other medications.
Effects on survival and development of the unborn child	There are no data from the use of Lynparza in pregnant women. Animal studies have shown that Lynparza causes adverse effects on the survival and the development of the fetus. Therefore, women of childbearing potential must use effective contraception during treatment with Lynparza and for 1 month after receiving the last dose of Lynparza. It is not known whether Lynparza may affect the effectiveness of some oral contraceptives and therefore additional non-hormonal contraceptive methods should be used. Pregnancy tests should be carried out before starting Lynparza and at regular intervals during treatment. Women of childbearing potential should not become pregnant while taking this medicine and not be pregnant at the beginning of treatment.

Missing information

Risk	What is known
Use with other medicinal products, including herbal products and other traditional remedies	Patients taking certain types of medicines or herbal products that could alter the way Lynparza is removed from the body were not allowed to participate in the Lynparza clinical studies. Patients are advised to tell their doctor about any other medication being taken, including vitamins and nutritional supplements. There are certain medications that should also be avoided if possible: - Itraconazole (used to treat fungal infections) - Telithromycin, clarithromycin (used to treat bacterial infections) - Boosted protease inhibitors, nelfinavir, indinavir, saquinavir, boceprevir, telaprevir, nevirapine (used to treat viral infections, primarily HIV) - Rifampicin, rifapentine, rifabutin (used to treat bacterial infections, primarily tuberculosis) - Phenytoin, carbamazepine, phenobarbital (used as a sedative or to treat seizures and epilepsy) - St John's wort (a herbal remedy used mainly for depression), herbal products and other traditional remedies. It is possible that the blood levels of Lynparza , or of other medicines, may be affected (either increased or decreased), when given together. Changes in blood levels of any drug may reduce its effectiveness or increase side effects.

Risk	What is known
	Certain types of medicines may be affected by Lynparza e.g., statins and hormonal contraceptives. It is therefore important that patients tell their doctor about all medications they are taking.
Use in patients with reduced liver or kidney function	Lynparza is removed from the body by the kidney and liver, therefore patients with reduced kidney or liver function might not be able to remove olaparib from the body as effectively as patients with normal kidney and liver function, possibly resulting in higher blood levels of olaparib and increased side effects. Lynparza is not recommended for use in patients with moderate or severely reduced kidney function, or in patients with reduced liver function.
Use in older patients >65 years	Most of the patients in the Lynparza clinical studies were less than 65 years old. The types and number of side effects in patients younger than 65 years were similar to those in patients aged 65 years and older, except that the older patients tended to have slightly more severe side effects. However, this difference was small and patients aged 65 years and older should be treated with Lynparza at the same dose as patients younger than 65 years.
Use in ethnically diverse groups	Over 9 in 10 of all patients who have been treated with Lynparza in clinical studies to date were white. There are very little data available on patients of other racial or ethnic groups. However the dose of Lynparza is the same for all racial and ethnic groups.
Long-term treatment with Lynparza /potential toxicity to Lynparza	There is limited data available for patients who have taken Lynparza treatment for longer than 2 years. Therefore, side effects following long-term treatment with Lynparza are not known. In the main clinical study, 24% (32 out of 136) of patients remained on maintenance treatment at 2 years.
Use in patients capable of only limited self-care or patients who cannot carry out any self-care.	There are no data available for patients whose performance status is poor, that is patients who are capable of only limited self-care, confined to a bed or chair more than 50% of waking hours or patients who are completely disabled who cannot carry out any self-care and are totally confined to bed or chair.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as ‘routine risk minimisation measures’.

The SmPC and the package leaflet are part of the medicine’s product information. The product information for Lynparza can be found on Lynparza’s EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study D0816C00008 A study of the effect of another medicine called rifampicin which is also broken down by enzymes in the liver, on the blood levels of olaparib	To investigate the effect of rifampicin on the blood levels of olaparib after oral dosing of olaparib tablets. To further investigate safety and effectiveness of olaparib in patients with cancer.	To provide information on the effect of certain types of medicines on the blood levels of olaparib.	Ongoing	Interim report available 3Q 2014. Final report Q3 2015.
Study D0816C00005 A study of olaparib in patients with normal and reduced liver function	To investigate the effect of mild or moderately reduced liver function on blood levels, safety and tolerability of olaparib in cancer patients, compared with patients with normal liver function.	To provide information on the use of olaparib in patients with reduced liver function.	Ongoing	Interim report estimated to be available by Q2 2015. Final report by Q1 2016.
Study D0816C00006 An study of olaparib in patients with normal and reduced kidney function	To investigate the effect of mild or moderately reduced kidney function on blood levels, safety and tolerability of olaparib in cancer patients, compared with patients with normal kidney function. Plasma and urine samples from this study will be used to identify breakdown	To provide information on the use of olaparib in patients with reduced kidney function.	Ongoing	Interim report estimated to be available by Q2 2015. Final report by Q1 2016.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	products of olaparib.			
Study D0816C00007 A study of the effect of a medicine called itraconazole on the blood levels of olaparib and a study of changes in electrical activity in the heart following olaparib tablet dosing.	To investigate the effects on blood levels of olaparib when given together with itraconazole. To further investigate safety and tolerability of olaparib tablets in patients with cancer. To investigate changes in the electrical activity of the heart following olaparib dosing.	To provide information on the effect of certain types of medicines on the blood levels of olaparib. To confirm whether olaparib affects the electrical activity of the heart.	Ongoing	Interim report available September 2014. Final report Q2 2015.
Study D0818C00001 A study of the safety and effectiveness of olaparib tablets in the treatment of women with ovarian cancer who have certain changes in their BRCA1 or BRCA2 genes (mutations)	To investigate the safety and effectiveness of olaparib in women with advanced ovarian cancer who have BRCA1 or BRCA2 mutations, and whose cancer has responded (reduced in size or disappeared) following one course of treatment with platinum-based chemotherapy.	Further evidence of efficacy and safety in patients with BRCA mutations. To provide additional safety data to gain more information about important identified risks, important potential risks, and missing information.	Started	Initial data estimated to be available by the end of 2016. Final data estimated to be available Q2 2020.
Study D0816C00002 A study of the safety and effectiveness of olaparib tablets in the treatment of women with	To investigate the safety and effectiveness of olaparib in women with ovarian cancer who have had at least two courses of	To gain further evidence of efficacy and safety in patients with BRCA mutations. To provide additional safety data to gain more	Started	Initial data estimated to be available Q1 2016. Final data estimated to be available Q4 2018.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
ovarian cancer who have certain changes in their BRCA1 or BRCA2 genes (mutations)	treatment with platinum-based chemotherapy and whose cancer has responded (reduced in size or disappeared) to the most recent course of chemotherapy.	information about important identified risks, important potential risks, and missing information.		
Study D0816C0000X A phase IV, open label, single arm, non randomised, multicentre study to assess the efficacy and safety of olaparib maintenance monotherapy in patients with relapsed platinum sensitive ovarian cancer who are in complete or partial response following platinum based chemotherapy and who carry loss of function germline or somatic BRCA mutation(s).	To investigate the safety and effectiveness of olaparib tablets in women with ovarian cancer who have previously responded to platinum based chemotherapy. Patients to be enrolled in the study are those who carry a BRCA mutation.	To gain further evidence of efficacy and safety in patients with somatic (acquired) or germline (inherited) BRCA mutations. To provide additional safety data to gain more information about important identified risks, important potential risks, and missing information.	Planned	Initial data estimated to be available Q1 2018. Final data estimated to be available Q3 2018.
Study D0810C00019 A study of the safety and effectiveness of olaparib (capsule) in the treatment of women with ovarian cancer that is sensitive to platinum chemotherapy	To investigate the safety and effectiveness of olaparib in women with ovarian cancer who have had at least two courses of treatment with platinum-based chemotherapy and whose cancer has	Further evidence of efficacy and safety in somatic BRCA (germline and somatic patients). To provide additional safety data to gain more information about important identified risks,	Started	Final data estimated to be available middle of 2017.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
following treatment with 2 or more platinum containing treatments	responded (reduced in size or disappeared) to the most recent course of chemotherapy.	important potential risks, and missing information.		
D081CC00006 A study of the safety and effectiveness of olaparib tablets compared with placebo (an inactive medication that looked identical to the olaparib tablet) in reducing the risk of breast cancer coming back in women who have certain changes in their BRCA1 or BRCA2 genes (mutations) and have a type of cancer known as 'Her2 negative (triple negative breast cancer).	To investigate if olaparib can reduce the risk of breast cancer coming back once all standard adjuvant anticancer treatments have finished.	To provide additional safety data to gain more information about important identified risks, important potential risks, and missing information.	Started	Initial data estimated to be available middle of 2020, final data 2028.
D0819C00003 A study of the safety and effectiveness of olaparib tablets compared with the doctor's choice of chemotherapy treatment in the treatment of women with metastatic breast cancer who have certain changes in their BRCA1 or BRCA2 genes	To investigate the safety and effectiveness of olaparib compared to the physician's choice of chemotherapy (capecitabine, vinorelbine or eribulin) in women with metastatic breast cancer who have BRCA1 or BRCA2 mutations who have not had more than 2	To provide additional safety data to gain more information about important identified risks, important potential risks, and missing information.	Started	Initial data estimated to be available Q3 2016, final data early 2018.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
(mutations)	courses of treatment with chemotherapy.			
Study number: To be confirmed A study to collect data over time from a large patient group with ovarian cancer, to gain more information about the risk of developing MDS/AML.	A study that follows over time a group of individuals (cohorts) who have ovarian cancer and who share important disease factors, to collect information about the risk of developing MDS/AML in real world conditions of clinical practice. Patients will be treated with approved medicines. The medicines are selected by the patients' own doctor in agreement with the patients; the treatment may include olaparib. A study synopsis will be submitted within 3 months of marketing approval.	To provide additional safety information about the important potential risk of MDS/AML in patients treated in clinical practice with existing medicines for ovarian cancer and patients treated with olaparib.	Planned	Data estimated to be available Q3 2020.

Studies which are a condition of the marketing authorisation

Three of the above studies (Study D0816C00002, D0810C00019, and D0816C0000X) are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 11-2014.