Summary of Risk Management Plan for Talazoparib

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

Talazoparib's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how talazoparib should be used.

I. The Medicine and What It Is Used For

Talazoparib is proposed to be used for the treatment of adult patients with germline BRCA mutated HER2-negative locally advanced or metastatic breast cancer (see SmPC for the full indication). It contains talazoparib as the active substance. The recommended dose of talazoparib is 1 mg capsule taken orally once daily, for which 1 mg hard capsules are available. Talazoparib is also available as 0.25 mg hard capsules to allow dose reductions to 0.75 mg, 0.5 mg, and 0.25 mg talazoparib.

Further information about the evaluation of talazoparib's benefits can be found in talazoparib's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/talzenna.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of talazoparib is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of talazoparib 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 talazoparib. 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.

Table 1. List of important risks and missing information

Important identified risks	None
Important Potential Risks	Myelodysplastic syndrome/Acute myeloid leukaemia (MDS/AML)
	Second primary malignancies (other than MDS/AML)
	Reproductive and developmental toxicity
Missing Information	None

II.B. Summary of Important Risks

Table 2. Important Potential Risk 1: Myelodysplastic syndrome/Acute myeloid leukaemia

Evidence source and strength of evidence	Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in patients who received PARP inhibitors. In the pivotal randomized breast cancer study, MDS/AML was not reported for any patients who received talazoparib and in 1 out of 126 (0.8%) patients in the chemotherapy treatment arm. Overall, MDS/AML has been reported in 1 out of 561 (0.2%) solid tumor patients treated at any dose with talazoparib in clinical studies. Evidence is confounded by prior exposure to other chemotherapeutic agents that may increase risk, and the inability to rule out the possibility of occurrence of MDS/AML that is unrelated to treatment with talazoparib.
Risk factors and risk groups	Patients previously treated with chemotherapy regimens, such as alkylating agents and anthracyclines, are at increased risk of developing leukaemia, which is further enhanced by the use of radiotherapy. Several studies have reported an increased incidence of AML after treatment of breast cancer, and it is estimated that 1 in every 20 patients will develop a secondary non-breast cancer after 10 years, which corresponds to a 22% increase of relative risk, particularly for secondary AML and MDS. The latency between primary diagnosis and therapy-related disease ranges from few months to several years, with a median of about two years, depending in part on the cumulative dose and/or the dose-intensity of the preceding cytotoxic therapy, as well on the exposure to specific agents. Therapy-related MDS/AML account for 10–20% of all cases of AML, the majority being non-treatment-related conditions. There are no known specific preventive measures to reduce the risk of MDS/AML in patients treated with talazoparib. For detection, complete blood count should be monitored for cytopenia or clinically significant changes during treatment. If MDS/AML is confirmed, talazoparib should be discontinued and supportive treatment provided.

Table 2. Important Potential Risk 1: Myelodysplastic syndrome/Acute myeloid leukaemia

Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.4, where advise is given to discontinue talazoparib if MDS/AML is confirmed - Package leaflet section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Table 3. Important Potential Risk 2: Second Primary Malignancies (other than MDS/AML)

Evidence source and strength of evidence	Amongst patients who received talazoparib at the proposed starting dose of 1 mg once daily, there were 6 patients who experienced 7 second primary malignancy adverse events (excluding MDS/AML), and none amongst patients who received talazoparib at doses other than 1 mg once daily. In comparison, 1 case of second primary malignancy (Malignant melanoma) was reported in the PCT arm (N=126; 0.8%) of Study 673-301 (EMBRACA). Evidence is confounded by prior exposure to other chemotherapeutic agents that may increase risk, and the inability to rule out the possibility of occurrence of second primary malignancies (other than MDS/AML) unrelated to treatment with talazoparib.
Risk factors and risk groups	Patients previously treated with chemotherapy regimens, such as alkylating agents and anthracyclines, are at increased risk of developing second primary malignancies (other than MDS/AML), which is further enhanced by the use of radiotherapy. The incidences of second primary malignancies (other than MDS/AML) after first primary breast cancer are higher than the general population and have been estimated in several cohort studies, where rates range from 0.24 to 0.83 per 100 Patient-Years. Rates may vary due to various factors, including malignancy type definitions, cancer sites included, patient inclusion criteria, treatment patterns, and clinical approaches to follow up. There are no known specific preventive measures to reduce the risk of second primary malignancies (other than MDS/AML) in patients treated with talazoparib. Patients being treated with talazoparib should be monitored for new onset malignancies as per standard clinical practice.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3 which provides in-vitro and in-vivo mutagenesis results Additional risk minimisation measures: None

Table 3. Important Potential Risk 2: Second Primary Malignancies (other than MDS/AML)

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Table 4. Important Potential Risk 3: Reproductive and Developmental Toxicity

Evidence source and strength of evidence	Based on findings from animal studies, talazoparib can cause embryo-foetal harm and may compromise male and female fertility. There are no available clinical data on talazoparib use in pregnant women or any clinical effects on fertility to inform a drug-associated risk.
Risk factors and risk groups	Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving talazoparib. A highly effective method of contraception is required for patients and partners of patients during treatment with talazoparib.
Risk minimisation measures	Routine risk minimisation measures: - SmPC Section 4.4, 4.6 where advice is given regarding use of contraception in male and female patients. - Package leaflet Section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Pregnancy follow-up questionnaires (Exposure During Pregnancy Supplemental Forms) will be utilized to collect further data on this safety concern. Additional pharmacovigilance activities: None

II.C. Post-Authorisation Development Plan

Not applicable.

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of talazoparib.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no studies required for talazoparib.