SUMMARY OF THE EU RISK MANAGEMENT PLAN
FOR
TALZENNA (TALAZOPARIB)
IN SWITZERLAND

This RMP summary for Switzerland is based on Part VI of the EU RMP for Talzenna (talazoparib), version 0.2, dated 27 November 2018

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INTRODUCTION

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 for talazoparib 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 marketing authorization. Please note that the reference document which is valid and relevant for the effective and safe use of talazoparib in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorised by Swissmedic.

Pfizer is fully responsible for the accuracy and correctness of the content of this published summary RMP for talazoparib.

OVERVIEW OF DISEASE EPIDEMIOLOGY

Breast cancer is the most common invasive cancer in women worldwide, representing 25.2% of new cancer cases, with nearly 1.7 million cases diagnosed in 2012. In the 28 States of the European Union (EU-28), there were an estimated 361,608 new cases of female breast cancer in 2012, corresponding to an age-adjusted annualized incidence of 80.3 per 100,000 females. In the US, there were an estimated 255,180 new breast cancer cases (females: 252,710; males: 2,470) in 2017. The age-adjusted annualized incidence was 124.9 per 100,000 females, representing 15% of all new cancer cases.

No studies were identified that reported incidence rates for gBRCAm locally advanced or metastatic breast cancer. However, several population-based studies were identified that evaluated the proportion of gBRCA mutation in invasive breast cancers, without regard to stage. These results are summarized in Table 1. Most of these studies were conducted in populations with a predisposition for gBRCAm, such as younger women, women with a family history of breast or ovarian cancers, or women referred for genetic testing. In a Danish study of women with breast cancer who were referred to clinical genetics for testing, 17.2% had a gBRCA mutation. Among populations of women enriched for genetic risk factors, such as early age of onset or family history, the prevalence of gBRCAm ranged from 4.1% to 9.1%. One US study reported that 4.2% of women with breast cancer and no affected first or second degree relatives had gBRCAm. In the same study, 8.3% of women with breast cancer and a first or second degree relative had gBRCAm.
Table 1. Proportion of gBRCA Mutations in Breast Cancer Patients in Population-based Studies

<table>
<thead>
<tr>
<th>Region or Country</th>
<th>Study Years</th>
<th>N</th>
<th>Study Design/Data Source</th>
<th>Study Population</th>
<th>gBRCAm</th>
</tr>
</thead>
<tbody>
<tr>
<td>International: Canada, US, and Australia⁶</td>
<td>1995-2000</td>
<td>3220</td>
<td>Population-based cohort study/cancer registries</td>
<td>Women with invasive breast cancer with evidence for increased genetic susceptibility</td>
<td>5.1% (n=165)</td>
</tr>
<tr>
<td>International: US and Denmark⁶</td>
<td>1985-2000</td>
<td>1394</td>
<td>Population-based, case-control study/cancer registry</td>
<td>Women aged &lt;55 with unilateral localized invasive breast cancer</td>
<td>5.2% (n=73)</td>
</tr>
<tr>
<td>Denmark⁷</td>
<td>2004-2011</td>
<td>523</td>
<td>Population-based cohort study/medical registries</td>
<td>Women with breast cancer who were referred to clinical genetics for gBRCAm testing</td>
<td>17.2% (n=90)</td>
</tr>
<tr>
<td>France⁸</td>
<td>1995-1997</td>
<td>232</td>
<td>Prospective population based cohort study/breast cancer registry</td>
<td>Women aged &lt;46 with early onset invasive breast cancer</td>
<td>9.1% (n=21)</td>
</tr>
<tr>
<td>UK⁹</td>
<td>1992-1993</td>
<td>254</td>
<td>Population-based, case-control study/cancer registries</td>
<td>White women aged &lt;36 with early onset breast cancer diagnosis between 1982-1985</td>
<td>5.9% (n=15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>363</td>
<td>Population-based, case-control study/cancer registries</td>
<td>White women aged 36-45 with early onset breast cancer diagnosis between 1988-1989</td>
<td>4.1% (n=15)</td>
</tr>
<tr>
<td>US¹⁰</td>
<td>1994-1998</td>
<td>1628</td>
<td>Population-based case-control study/cancer registries and hospital records</td>
<td>White and Black women aged 35-64 with invasive breast cancer</td>
<td>5.9% (n=96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>429</td>
<td></td>
<td>Sample enriched for family history</td>
<td>4.2% (n=18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>860</td>
<td></td>
<td>No family history of breast cancer</td>
<td>8.3% (n=71)</td>
</tr>
<tr>
<td>US¹¹</td>
<td>1989-1994</td>
<td>54</td>
<td>Population-based series/hospital and health-care facility records</td>
<td>Men with breast cancer</td>
<td>3.7% (n=2)⁸</td>
</tr>
</tbody>
</table>

a. No gBRCA1 mutations were identified.
The lack of robust population-based estimates of the proportions of breast cancers that are gBRCAm precludes estimating the incidence using annualized US or EU incidence rates.

**TREATMENT INDICATION**

Talazoparib is a potent, small-molecule inhibitor of Poly Adenosine Diphosphate (ADP) Ribose Polymerase (PARP) enzymes, PARP1 and PARP2. PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, cell cycle regulation and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by two mechanisms, inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription and ultimately leading to apoptosis and/or cell death. The potent cytotoxicity observed with talazoparib against multiple tumour cell lines harbouring mutations in the DDR pathways, can be attributed to its inhibition of PARP catalytic activity and robust PARP trapping.

Talazoparib is proposed to be used for the treatment of adult patients with germline BRCA mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

**UNKNOWNWS RELATING TO TREATMENT BENEFITS**

The treatment benefit of talazoparib has not been studied in pregnant or breastfeeding women, immuno-compromised patients, subpopulations carrying known and relevant genetic polymorphisms, or in patients with severe renal impairment or requiring hemodialysis.

**SUMMARY OF SAFETY CONCERNS**

**Important Identified Risks:** none

**Important Potential Risks:** see Table 2
Table 2. Important Potential Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplastic syndrome/Acute myeloid</td>
<td>Talazoparib was clastogenic in in vitro chromosomal aberration and in vivo micronucleus assays, indicating potential for genotoxicity in humans. Patients previously treated with chemotherapy regimens, such as alkylating agents and anthracyclines, are at increased risk of developing leukemias, 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 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.</td>
</tr>
<tr>
<td>leukemia (MDS/AML)</td>
<td></td>
</tr>
<tr>
<td>Second primary malignancies (other than</td>
<td>Talazoparib was clastogenic in in vitro chromosomal aberration and in vivo micronucleus assays, indicating potential for genotoxicity in humans. Patients previously treated with chemotherapy regimens, such as alkylating agents and anthracyclines, are at increased risk of developing second primary malignancies, which is further enhanced by the use of radiotherapy. The incidences of second primary malignancies 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. In addition, an underlying increased risk of ovarian cancer may be present in patients with mutated gBRCA.</td>
</tr>
<tr>
<td>MDS/AML)</td>
<td></td>
</tr>
<tr>
<td>Reproductive and developmental toxicity</td>
<td>Talazoparib was clastogenic in in vitro chromosomal aberration and in vivo micronucleus assays, indicating potential for genotoxicity in humans. 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 include women of childbearing potential, pregnant women, and lactating women.</td>
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<td></td>
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</tbody>
</table>

Missing Information

Table 3. Missing Information

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in severe renal impairment</td>
<td>Given the limited data available for patients with severe renal impairment treated with talazoparib (only 1 patient), the difference, if any, in the safety profile of patients with normal renal function versus those who have severe renal impairment among patients in the proposed indication is not known. A formal renal impairment study to evaluate the PK and safety profile of talazoparib multiple daily oral doses of 0.5 mg in patients with varying renal impairment is not available.</td>
</tr>
</tbody>
</table>

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Table 3.  Missing Information

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is Known</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>degrees of renal impairment as compared to patients with normal renal function is currently ongoing.</td>
</tr>
</tbody>
</table>

SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

All medicines have a product information ("Fachinformation/Information professionelle") which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (patient information; “Patienteninformation/Information destinée aux patients”). The measures in these documents are known as routine risk minimisation measures.

The product information and the information for patients on talazoparib can be found on www.swissmedicinfo.ch.

This medicine has no additional risk minimisation measures.

PLANNED POST AUTHORISATION DEVELOPMENT PLAN

Not applicable.

Studies that are a Condition of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation.

SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not applicable.
REFERENCES


