

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211651Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211651
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Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
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Review Completion Date	October 5, 2018
Subject	Review to determine if a REMS is necessary
Established Name	Talazoparib
Trade Name	Talzenna
Name of Applicant	Pfizer Inc.
Therapeutic Class	Poly (ADP-ribose) polymerase (PARP) inhibitor
Formulation(s)	0.25 mg and 1 mg capsules
Dosing Regimen	1 mg taken as a single oral daily dose, with or without food, until disease progression or unacceptable toxicity occurs.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity talazoparib (Talzenna) is necessary to ensure the benefits outweigh its risks. Pfizer Inc. submitted a New Drug Application (NDA) 211651 for talazoparib with the proposed indication for the treatment of adult patients with germline BRCA (gBRCA)-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. The serious risks associated with the use of talazoparib are myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), myelosuppression, and embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Information.

DRISK and the Division of Oncology Products I (DOP I) have determined that if approved, a REMS is not necessary to ensure the benefits of talazoparib outweigh its risks. The treatment of patients with advanced breast cancer (locally advanced not amenable to curative treatment and metastatic disease) is palliative in nature. Most of the current treatment guidelines for HER2-negative breast cancer do not specifically address the presence of BRCA mutations, and treatment options specifically tailored for BRCA-mutated breast cancer remain limited. Despite the availability of new therapies, the long-term prognosis for patients with MBC is poor and there is a clear need for new treatments for patients with deleterious or suspected deleterious gBRCA-mutated HER2 negative locally advanced or MBC. In the clinical trial, talazoparib appeared efficacious in both its primary and secondary outcomes. The most concerning adverse reaction associated with the use of talazoparib are MDS/AML, myelosuppression and embryo-fetal toxicity. Similar to other poly (ADP-ribose) polymerase (PARP) inhibitors, olaparib, rucaparib, and niraparib, if approved, these risks will be communicated in the Warnings and Precautions section of the label, as well as information regarding MDS/AML to be included in section 17, Patient Information, to inform patients and increase the prominence of this information and promote its mitigation.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) talazoparib (Talzenna) is necessary to ensure the benefits outweigh its risks. Pfizer Inc. submitted a New Drug Application (NDA) 211651 for talazoparib with the proposed indication for the treatment of adult patients with germline BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.¹ This application is under review in the Division of Oncology Products I (DOP I). The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Information.

2 Background

2.1 PRODUCT INFORMATION

Talazoparib is a NME NDA type 505(b)(1) pathway application.^a It is a poly (ADP-ribose) polymerase (PARP) inhibitor, proposed for indication as treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer.^{1,2} The PARP family of proteins is involved in repair of single-strand DNA breaks. PARP inhibition may lead to the accumulation PARP-DNA complexes and single-strand breaks that give rise to double-strand DNA breaks during DNA replication. These double-strand breaks may lead to DNA damage, which is potentiated by loss of function of homologous recombination repair enzymes such as BRCA. The induced DNA damage may lead to the initiation of apoptotic pathways and cell death.^{1,3} In addition, talazoparib causes PARP trapping. PARP trapping is the mechanism of action where the PARP molecule is trapped on the DNA, which interferes with the cell's ability to replicate.^{2,3} The recommended dose of talazoparib is 1 mg taken as a single oral daily dose, with or without food, until disease progression or unacceptable toxicity occurs.^b Talazoparib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for talazoparib (NDA 211651) relevant to this review:

- 11/12/2010: Investigation New Drug (IND) 108708 submission was received.
- 04/06/2018: NDA 211651 submission for talazoparib with the proposed indication for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer, received.
- 07/23/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that safety review is ongoing and at this time, the review teams have not identified a need for a REMS for talazoparib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Breast cancer is the second leading cause of cancer death in women.^c The chance that a woman will die from breast cancer is about 1 in 36 (about 3%). The American Cancer Society estimates that approximately 266,120 new cases of invasive breast cancer will be diagnosed in women in United

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

States^d, and about 40,920 women will die from breast cancer in 2018.⁴ Breast cancer is a molecularly diverse disease with several clearly defined molecular subgroups.⁵ Clinically, however, three therapeutic groups are used: those classified as hormone receptor-positive, those classified as HER2-positive, and those classified as triple-negative. The predominant subset is HR-positive, HER2-negative disease. Of the new breast cancer cases diagnosed worldwide each year, roughly 60% to 65% are HR-positive, 20% to 25% are HER2-positive, and 15% to 18% are triple-negative.⁶ Approximately 5% of breast cancers are associated with a mutation in the breast cancer susceptibility gene (BRCA1 and/or BRCA2 gene). Approximately 70% of BRCA1 mutated breast cancers present as triple negative breast cancer (TNBC). In contrast, breast cancer patients carrying mutations in the BRCA2 gene are more likely to be positive for expression of the estrogen receptor (ER) and progesterone receptor (PgR) and approximately 20% are triple-negative.³ About 55% to 65% of women who inherit a BRCA1 mutation and approximately 45% of women who inherit a BRCA2 mutation will develop breast cancer by age 70.⁷ The women with specific *BRCA1/BRCA2* mutations who develop breast cancer are at increased risk for death from their disease, particularly if the mutation is in *BRCA1*. For up to 10 years after diagnosis, the risk for metachronous ipsilateral cancer is similar to that in women without mutations, but the risk for contralateral disease is substantially higher.⁸ The expression profile of biological markers in breast cancer is correlated with prognosis and response to treatment, and therefore plays an important role in treatment decisions.⁹

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The treatment of patients with advanced breast cancer (locally advanced not amenable to curative treatment and metastatic disease) is palliative in nature.¹⁰ Endocrine therapy is preferable to chemotherapy for patients with hormone receptor (HR)-positive metastatic breast cancer (MBC), provided there is no visceral crisis. Other treatment options for patients with HR-positive MBC include endocrine therapy in combination with CDK 4/6 inhibitors. Most patients with HR-positive MBC will eventually require cytotoxic chemotherapy either as initial treatment or following endocrine therapies. FDA-approved endocrine therapies available for HR-positive MBC include tamoxifen, anastrozole, letrozole, toremifene, exemestane, and fulvestrant. In addition, everolimus has been approved in combination with exemestane, palbociclib has been approved in combination with letrozole or fulvestrant, abemaciclib has been approved in combination with fulvestrant, and ribociclib has been approved in combination with letrozole.^{3,11,12}

For patients with triple negative MBC, there is no single preferred first line chemotherapy. Sequential monotherapy with single-agent chemotherapy is preferred, with combination chemotherapy reserved for patients with rapid clinical progression, life threatening visceral metastases, or need for rapid symptom and/or disease control. For patients previously treated with an anthracycline and a taxane in the adjuvant or metastatic setting, FDA-approved cytotoxic chemotherapy options include gemcitabine, capecitabine, ixabepilone, and eribulin.¹² Olaparib is a PARP inhibitor approved by the FDA for the treatment in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.¹³ Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.¹²

^d Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

4 Benefit Assessment

The efficacy of talazoparib was evaluated in an open-label, randomized, multicenter clinical trial (Study EMBRACA; NCT01945775). The study population included 431 patients with gBRCAm HER2-negative locally advanced or metastatic breast cancer were randomized 2:1 to receive talazoparib 1 mg or healthcare provider’s choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) until disease progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (TNBC versus non-TNBC), and history of central nervous system (CNS) metastasis (yes versus no).¹

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for talazoparib. Efficacy was established on the basis of the progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by blinded independent central review (BICR).¹ A statistically significant improvement in PFS was demonstrated for talazoparib compared with chemotherapy is shown in Table 1.^{1,3,e} A sensitivity analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results. Consistent PFS results were observed across patient subgroups defined by study stratification factors (line of therapy, TNBC status, and history of CNS metastases). The estimated medians for IRF assessed PFS in the talazoparib and PCT arms were 8.6 months (95% CI: 7.2 – 9.3 months) and 5.6 months (95% CI: 4.2 – 6.7 months), respectively. The estimated hazard ratio was 0.54 (95% CI: 0.41 - 0.71). The results are statistically significant with a p-value less than 0.0001. Secondary efficacy endpoints include overall response rate (ORR) and overall survival (OS). The OS data were not mature at the time of the final PFS analysis (38% of patients had died). Response rates were 50.2% and 18.4% in the talazoparib and PCT arms, respectively. The estimated median duration of response (DOR) on the talazoparib arm was 6.4 months, 2.5 months longer than the median DOR in the PCT arm.³

Table 1. Summary of Efficacy Results – EMBRACA Study^{1,3,e}

	Talazoparib	Chemotherapy
Progression-Free Survival by BICR	N=287	N=144
Events, number (%)	186 (65)	83 (58)
Median months (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI) ^a	0.54 (0.41, 0.71)	
p-value ^b	p<0.0001	
Patients with Measurable Disease by Investigator ^c	N=219	N=114
Objective Response Rate, % (95% CI) ^d	50.2 (43.4, 57.0)	18.4 (11.8, 26.8)
Duration of Response Median ^e months (95% CI)	6.4 (5.4, 9.5)	3.9 (3.0, 7.6)
Abbreviations: BICR=blinded independent central review; CI=confidence interval. ^a Hazard ratio is estimated from a Cox proportional hazards model stratified by prior use of chemotherapy for metastatic disease (0 versus 1, 2, or 3), by triple-negative disease status (triple-negative breast cancer [TNBC] versus non TNBC), and by history of central nervous system metastasis (yes versus no). ^b P-values from stratified log-rank test (2-sided). ^c Conducted in intent-to-treat (ITT) population with measurable disease at baseline. ^d Response rate based on confirmed responses. ^e Median estimated from Kaplan-Meier probabilities.		

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for talazoparib. The safety analysis of talazoparib primarily focuses on 286 patients treated with talazoparib 1 mg/day in the phase 3 EMBRACA Study. The median duration of study treatment was 6.1 months in patients who received talazoparib and 3.9 months in patients who received chemotherapy.

The most common adverse reactions ($\geq 20\%$) of any grade were fatigue (62%), anemia (53%), nausea (49%), neutropenia (35%), headache (33%), thrombocytopenia (27%), vomiting (25%), alopecia (25%), diarrhea (22%), and decreased appetite (21%).¹

Deaths

There were a total of 15 deaths occurring within 30 days of last study treatment and 10 of these deaths were associated with an AE: 6 patients (2.1%) in the talazoparib arm and 4 patients (3.2%) in the PCT arm. The AEs associated with death in the talazoparib arm were general physical health deterioration (2 patients); and cerebral hemorrhage, liver disorder, neurological symptom, and VOD (1 patient each). There was one death associated with an AE in each treatment arm that was considered related to treatment: veno-occlusive liver disease (VOD) on the talazoparib arm and sepsis on the PCT arm. That patient who was thought to have died from VOD had developed asymptomatic Grade 2 ALT and AST increase with normal bilirubin followed 3 weeks later by Grade 3 liver test abnormalities (ALT and AST with normal bilirubin) while receiving talazoparib at 0.75 mg/day, approximately 6 months after initiating treatment and 1 month after the dose was increased from 0.5 mg/day. Talazoparib dosing was discontinued 10 days later due to Grade 4 thrombocytopenia. Ten days after talazoparib dosing was discontinued, the patient was admitted to a health care facility with acute hepatic failure attributed to VOD of the liver by the investigator. Concomitant medications at the time included naloxone/tilidine^{f,14} and metamizole. Sixteen days after the last dose of the study drug, the patient died due to Grade 5 suspected VOD of the liver. Clinical symptoms of VOD (such as hepatomegaly and right upper quadrant pain) were not noted. Autopsy was not performed. The cause of death was also reported as disease progression. The investigator assessed the events of thrombocytopenia and VOD as related to talazoparib. The Applicant assessed the acute hepatic failure as possibly related to talazoparib, noting that the assessment is confounded by the patient's progressive metastatic disease (notable for new onset malignant ascites and bilateral pleural effusions), possible sepsis (as suggested by an elevated procalcitonin), and possible disseminated intravascular coagulation or thrombotic thrombocytopenic purpura (as suggested by progressive thrombocytopenia with no decrease in WBCs and hemoglobin, and reduced fibrinogen and antithrombin III). Based on the information provided, the Applicant considered VOD an unlikely etiology, a consideration supported by 2 hepatologist consultants to the Applicant who reviewed the case. The clinical reviewer stated that the assessment appears reasonable.³

^f Tilidine (ValoronTM) is an orally effective opioid analgesic that was introduced in West Germany in 1970 and subsequently in other countries including Belgium, Mexico, and South Africa as a combination product with naloxone (Valoron NTM) in a ratio of 12.5:1 (50 mg tilidine combined with 4 mg naloxone).¹⁴

Serious Adverse Events (SAE)

The clinical reviewer stated that the overall incidence of SAEs was similar in the two treatment arms for EMBRACA. Anemia was the most common SAE (5.9%) in the talazoparib treatment arm and no cases in the chemotherapy arm. The SAEs seen with talazoparib treatment are similar to the known safety profile of PARP inhibitors. These mainly include hematologic events that can be managed by dose interruption and/or reduction, as well as supportive care therapies.³ Dosing interruptions due to an adverse reaction of any grade occurred in 65% of patients receiving talazoparib and 50% of those receiving chemotherapy; dose reductions due to any cause occurred in 53% of talazoparib patients and 40% of chemotherapy patients. Permanent discontinuation due to adverse reactions occurred in 13 (5%) talazoparib patients and 7 (6%) chemotherapy patients.¹

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 MYELOYDYSPLASTIC SYNDROME/ACUTE MYELOID LEUKEMIA

Labeling will note that Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received talazoparib, with MDS/AML reported in 2 out of 584 (0.3%) solid tumor patients treated with talazoparib in clinical studies. As described in the label, the duration of treatment with talazoparib in these two patients prior to developing MDS/AML was 4 months and 24 months, respectively. Both patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy. Labeling instructs prescribers to monitor complete blood counts for cytopenia at baseline and monthly thereafter and further advises that for prolonged hematological toxicities, talazoparib should be interrupted and blood counts monitored weekly until recovery. If MDS/AML is confirmed, labeling instructs to discontinue talazoparib. Besides being communicated in the Warnings and Precautions section of the label, this information will also be included in section 17, Patient Information, to inform patients and increase the prominence of this information, as well as to promote its mitigation.¹

5.2 MYELOSUPPRESSION

Myelosuppression consisting of anemia, leukopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with talazoparib. Grade ≥ 3 anemia (39%), neutropenia (21%), and thrombocytopenia (15%) were reported in patients receiving talazoparib. Discontinuation occurred in 0.7%, 0.3%, and 0.3% of patients due to anemia, neutropenia, and thrombocytopenia, respectively. To mitigate this risk, labeling instructs prescribers to monitor complete blood count for cytopenia at baseline and monthly thereafter and further instructs them not to start talazoparib until patients have adequately recovered from hematological toxicity caused by previous therapy. Monitoring and dosage modifications for toxicities to address the safety issues with talazoparib will also be included in the Dosage and Administration section of the label.¹

5.3 EMBRYO-FETAL TOXICITY

Similar to other PARP inhibitors, based on its mechanism of action and findings from animal data, talazoparib can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, administration of talazoparib to pregnant rats during the period of organogenesis caused fetal malformations and structural skeletal variations, and embryo-fetal death at exposures that were 0.24 times the area under the concentration-time curve (AUC) in patients receiving the recommended human

dose of 1 mg daily. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception during treatment with talazoparib and for a specified time dependent on the patient's sex after the last dose will be communicated in the Use in Specific Populations section of the label.¹

6 Expected Postmarket Use

The proposed indication is for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer. It is expected that oncologists, who should be familiar with the management of chemotherapeutic toxicities such as MDS/AML, myelosuppression, and embryo-fetal toxicity, will be the likely prescribers of talazoparib in both inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for talazoparib beyond routine pharmacovigilance and labeling. The applicant proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Information to inform patients regarding the potential risks of MDS/AML.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for talazoparib, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Talazoparib is a PARP inhibitor, proposed for indication as treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer. Based on the efficacy and safety information currently available, the clinical reviewer recommended approval of talazoparib as a PARP inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2 negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for talazoparib^{g, 1,3}

DRISK and the DOP-I have determined that if approved, a REMS is not necessary to ensure the benefits of talazoparib outweigh its risks. Labeling, including Warnings and Precautions will be used to communicate the safety issues and management of toxicities associated with talazoparib. The most concerning adverse reactions observed with the use of talazoparib are MDS/AML, myelosuppression and embryo-fetal toxicity. Talazoparib appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.

The treatment of patients with advanced breast cancer (locally advanced not amenable to curative treatment and metastatic disease) is palliative in nature. Most of the current treatment guidelines for HER2-negative breast cancer do not specifically address the presence of BRCA mutations, and treatment

^g Labeling negotiations were ongoing at the time of completion of this review. Indication statement is updated and significant changes to the proposed label made by FDA prior to negotiations.

options specifically tailored for BRCA-mutated breast cancer remain limited. Olaparib is another PARP inhibitor approved by the FDA in January 2018 for the treatment in patients with deleterious or suspected deleterious gBRCAm, HER2-negative MBC who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Despite the availability of new therapies, the long-term prognosis for patients with MBC is poor. In light of the high burden of disease, there remains a clear medical need to develop new therapies for the treatment of MBC to extend life, delay disease progression and/or lessen breast cancer related symptoms and therefore talazoparib has the potential to fill this need in patients with deleterious or suspected deleterious gBRCA-mutated HER2 negative locally advanced or MBC.

Similar to other PARP inhibitors, olaparib¹³, rucaparib¹⁵ and niraparib¹⁶, labeling will include the risk of MDS/AML in the Warnings and Precautions section of the label, as well as in section 17, Patient Information to inform patients and to increase the prominence of this information and promote its mitigation. The risks of myelosuppression and embryo-fetal toxicity will likely be communicated in the Warnings and Precautions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with talazoparib will be included in the Dosage and Administration and Warnings and Precautions sections of the label. At this time, none of these risks will receive a boxed warning in the label.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of talazoparib. The management of the risks associated with talazoparib treatment can be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

- ¹ Proposed Prescribing Information for talazoparib as currently edited by the FDA, last updated September 28, 2018.
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- ¹⁴ Fudala PJ, Johnson RE. Development of opioid formulations with limited diversion and abuse potential. *Drug Alcohol Depend.* 2006;83 Suppl 1:S40-47.
- ¹⁵ Rubraca. Prescribing Information (last updated 04/2018).
- ¹⁶ Zejula. Prescribing Information (last updated 03/2017).

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/s/

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