

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208447Orig1s000

**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
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Reviewer Name(s)	Elizabeth Everhart, MSN, ACNP
Team Leader	Doris Auth, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 7, 2017
Subject	Evaluation of Need for a REMS
Established Name	Niraparib
Trade Name	Zejula
Name of Applicant	Tesaro, Inc.
Therapeutic Class	poly(ADP-ribose) polymerase (PARP) 1 and 2 inhibitor
Formulation(s)	100 mg capsule
Dosing Regimen	300 mg daily

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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 Zejula (niraparib) is necessary to ensure the benefits of this product outweigh its risks. Tesaro, Inc. (Tesaro) submitted a New Drug Application (NDA) 208447 for niraparib with the proposed indication of the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. The serious risks associated with the use of niraparib include the risk of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), bone marrow suppression, hypertension, including hypertensive crisis and potential embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Advanced ovarian cancer is a life-threatening condition with poor five-year median survival; there is an unmet medical need for these patients. The niraparib treatment group had a significantly prolonged median PFS over the placebo regimen; this was a clinically meaningful benefit to patients with advanced ovarian cancer. If approved, similar to Lynparza (olaparib) and Rubraca (rubaparib), two other poly (ADP-ribose) polymerase (PARP) inhibitors, the risks will be communicated through labeling. The Warnings and Precautions section of the professional labeling for niraparib will communicate the potential risks of MDS/AML, bone marrow suppression, and hypertension, including hypertensive crisis.

In conclusion, DRISK and the Division of Oncology (DOP I) agree that a REMS is not needed to ensure the benefits of niraparib outweigh its risks.

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)^a Zejula (niraparib) is necessary to ensure the benefits of this product outweigh its risks. Tesaro, Inc. submitted a New Drug Application (NDA #208447) for niraparib with the proposed indication of the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following a complete or partial response to platinum-based chemotherapy. This application is under review in the Division of Oncology Products I (DOP 1). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Niraparib, a new molecular entity, is a poly(ADP-ribose) polymerase (PARP) 1 and 2 inhibitor proposed for maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. Niraparib's proposed dosage is 300 mg orally per day (three 100 mg capsules) until disease progression or unacceptable adverse reaction.^b Niraparib is not currently approved in any jurisdiction.

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

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208447 relevant to this review:

- 10/14/2016: Breakthrough designation granted
- 11/16/2016: NDA 208447 submission for maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy received
- 12/16/2016: Priority review granted
- 02/10/2017: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for niraparib.

3 Therapeutic Context and Treatment Options

The typical course of treatment for ovarian cancer is often surgical de-bulking and platinum-based chemotherapy; it is effective at inducing an initial response, but ovarian cancer will recur in the majority of women. Once there is a recurrence, second-line platinum-based chemotherapy is given; for those patients who respond, the current standard of care is monitoring patients off therapy for disease progression and then re-treating them with platinum-based or other chemotherapy, with or without Bevacizumab¹. The response rate in these cases is quite low and the toxicities are severe and have a major impact on quality of life. Currently, there are no approved therapies for patients with advanced platinum-sensitive ovarian cancer following a response to second line chemotherapy. There is an unmet medical need in this setting.

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Ovarian cancer accounts for nearly 3 percent of all cancers in women and is the fifth leading cause of cancer-related death in women in the United States.^c In 2016, an estimated 22,000 women were diagnosed with ovarian cancer and approximately 14,000 died of the disease.^d Because ovarian cancer is often diagnosed at an advanced stage, it causes more cancer deaths than any other female reproductive system cancer.² While the 5-year overall survival rate for ovarian cancer is 46% across all stages it is only 29% in patients diagnosed with distant metastatic disease.³

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Surgical de-bulking followed by platinum-based chemotherapy is the standard of care⁴, with other platinum-based chemotherapy used in recurrent ovarian cancer and chemotherapies such as docetaxel, topotecan, pegylated liposomal doxorubicin, or paclitaxel used in recurrent, platinum-resistant ovarian

^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.*

^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.*

cancers. Two other PARP inhibitors, Lynparza (olaparib), approved in 2014, and Rubraca (rucaparib), approved in 2016, have received accelerated approval in the U.S. Lynparza is indicated for patients with germline BRCA (Breast Cancer) mutation-associated ovarian cancer who have received 3 or more prior chemotherapy regimens and Rubraca is indicated as monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies.

4 Benefit Assessment^e

The pivotal trial (PR-30-5011-C, also known as NOVA) supporting this application is a Phase 3, randomized, double-blind trial of maintenance with niraparib versus placebo in 553 (372 niraparib/181 placebo) patients with platinum-sensitive ovarian cancer. The study was designed to evaluate niraparib maintenance treatment in 2 cohorts of patients, those with germline BRCA mutation (gBRCAmut cohort) and those with high-grade serous or high-grade predominantly serous histology, but who were not germline BRCA mutation carriers (non-gBRCAmut cohort). Patients were prospectively assigned to a cohort based on the results of the Integrated BRCAAnalysis[®] test, conducted at a central laboratory. Within each cohort patients were randomized 2:1 to receive niraparib or placebo. Study PR-30-5011-C's primary endpoint was progression free survival (PFS), defined as the number of months between randomization and progression or death. The niraparib treatment group had a significantly prolonged median PFS over the placebo regimen.

The table⁵ below summarizes the results from the primary study endpoint. The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on an improvement in PFS.

Statistic	gBRCAmut Cohort		non-gBRCAmut Cohort	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
PFS Median in months (95% CI)	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)
p-value	<0.0001		<0.0001	
Hazard Ratio (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)	

5 Risk Assessment

The serious adverse events associated with niraparib are bone marrow suppression, cardiovascular effects (hypertension, including hypertensive crisis, tachycardia, tachyarrhythmias, angina pectoris and myocardial infarction), and myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML).^f These

^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.

^f Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the

serious adverse events will be discussed in the sections below. There were no on treatment deaths reported in the NOVA study, with 95 deaths occurring during the follow-up phase; of those deaths, 60 (16%) were among the 372 patients randomized to the niraparib arm and 35 (19%) were among the 181 patients randomized to the placebo arm. Three of the deaths reported during the follow-up phase were due to MDS/AML, including 2 patients randomized to the placebo arm and 1 patient randomized to the niraparib arm.

Niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow), and therefore has the potential to cause teratogenicity and/or embryofetal death. There are no data regarding the use of niraparib in pregnant women to inform the drug-associated risk⁶.

5.1 BONE MARROW SUPPRESSION

Hematologic adverse reactions including thrombocytopenia, neutropenia, and anemia have been reported with niraparib. Common Terminology Criteria for Adverse Events (CTCAE), Version 4, Grade ≥ 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving niraparib.

5.2 MYELODYSPLASTIC SYNDROME/ACUTE MYELOID LEUKEMIA

MDS/AML, including cases with fatal outcomes, have been reported in patients who received niraparib. In the NOVA study, MDS/AML occurred in 5 of 367 (1.4%) of patients who received niraparib, versus 2 of 179 (1.1%) of patients who received placebo. Across all studies, MDS/AML has been reported in 7 of 751 (0.9%) of patients treated with niraparib. Of the patients who developed MDS/AML, the duration of treatment with niraparib ranged from <1 month to > 2 years; all patients had received prior platinum-containing chemotherapy and some had also received other DNA-damaging agents and radiotherapy.

5.3 CARDIOVASCULAR EFFECTS

Hypertension and hypertensive were reported in patients treated with niraparib. In the NOVA study, CTCAE Grade 3-4 hypertension occurred in 9% of niraparib-treated patients compared to no placebo-treated patients.

Arrhythmias including atrial and ventricular tachycardia occurred in 9% of niraparib-treated patients compared to 2% of placebo-treated patients in the NOVA trial. The potential for QTc prolongation was evaluated in the NOVA study with the treatment dose of 300 mg once daily of niraparib and reviewed by FDA. No large changes in the mean QTc interval, >20 ms, were detected at the therapeutic dose of 300 mg once daily of niraparib.⁷

6 Expected Postmarket Use

Niraparib will be primarily prescribed in the outpatient setting by oncologists who should be familiar with the management of toxicities associated with PARP inhibitors. The prescribing information will address the risks associated with niraparib, including Warnings and Precautions regarding MDS/AML, bone marrow suppression, cardiovascular effects, including hypertension and hypertensive crisis, as well as drug.

as embryo-fetal toxicity. The PI will also include guidelines for patient monitoring and dose reductions/discontinuations as appropriate.

7 Risk Management Activities Proposed by the Applicant

Tesaro did not propose any risk management activities for niraparib beyond routine pharmacovigilance and labeling. The proposed labeling includes Warnings and Precautions to communicate the risks of MDS/AML, bone marrow suppression, cardiovascular effects, including hypertension, hypertensive crisis, and tachycardia, as well as embryo-fetal toxicity.

The labeling includes recommendations for monitoring and dose adjustments and/or discontinuation for patients who develop MDS/AML, bone marrow suppression, and cardiovascular events; the proposed PI further recommends medical management of hypertension with antihypertensive medications as appropriate. To manage bone marrow suppression, the proposed PI recommends that, in patients who received prior chemotherapy and experienced associated hematologic toxicity, niraparib should not be started until their hematologic parameters have returned to normal or within CTCAE grade 1. The proposed PI also includes a statement concerning embryo-fetal toxicity and avoiding pregnancy.

8 Discussion of Need for a REMS

When considering whether a REMS is necessary to ensure that the benefits outweigh the risks of a particular drug, DRISK considers factors such as the size of the patient population, the seriousness of the disease, the expected benefit of the drug, the seriousness of the known or potential adverse events, and the likely prescribers. Advanced ovarian cancer is a life-threatening condition with poor five-year median survival; the increase in PFS over placebo in the clinical studies is a clinically meaningful benefit to patients with advanced ovarian cancer. At the Mid-cycle meeting, the Clinical Reviewer recommended approval of niraparib on the basis of the efficacy and safety information currently available.

In December, 2014, Lynparza (olaparib) was granted accelerated approval; the label for Lynparza⁸ includes Warnings and Precautions regarding the risks of MDS/AML and pneumonitis. In December, 2016, Rubraca (rucaparib) was granted accelerated approval; the label for Rubraca⁹ includes Warnings and Precautions regarding the risks of MDS/AML and embryo-fetal toxicity.

Similar to other drugs in this class, the serious risks of MDS/AML, bone marrow suppression, and cardiovascular effects (hypertension, including hypertensive crisis, and tachycardia) will be communicated through labeling.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for niraparib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety and efficacy information, as well as labeling, was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

1. Tesaro. Draft Prescribing Information for Niraparib, February, 2017.
2. Tesaro. Clinical Overview for Niraparib, November, 2016.
3. Tesaro. Summary of Clinical Safety for Niraparib, November, 2016.
4. Wedam, Suparna. Division of Oncology Products I. Clinical Review for Breakthrough Designation for IND 100996, submitted to DARRTS on October 4, 2016.
5. Ison, Gwynn. Division of Oncology Products I. Mid-cycle clinical review slides, February 6, 2017.

11 REFERENCES

¹ Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ) – Health Professional Version, accessed 1/3/17, <https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq#section/ 82>

² A Snapshot of Ovarian Cancer; National Cancer Institute, accessed 1/3/17, <https://www.cancer.gov/research/progress/snapshots/ovarian> and <https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq#link/ 416 toc>.

³ SEER Stat Fact Sheets: Ovarian Cancer, National Cancer Institute, accessed 1/3/17, <https://seer.cancer.gov/statfacts/html/ovary.html>.

⁴ American Cancer Society, Inc. Cancer Facts & Figures 2016, Pg. 18.

⁵ Tesaro. Clinical Overview. Pg. 12.

⁶ Tesaro. Draft prescribing information for niraparib, February, 2017.

⁷ Dhananjay D. Marathe. Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, submitted to DARRTS on February 14, 2017.

⁸ Olaparib (Lynparza™) USPI, Revised October, 2016.

⁹ Rucaparib (Rubraca™) USPI, Revised December, 2016.

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/s/

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