

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206162Orig1s000

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

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: November 19, 2014

Reviewer: Naomi Redd, Pharm.D., Acting Team Leader
Division of Risk Management

Acting Division Director: Cynthia LaCivita, Pharm.D.
Division of Risk Management

Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Olaparib (Lynparza)

Therapeutic Class: Polyadenosine 5' diphosphoribose polymerase (PARP)
inhibitor

Dosage and Route: 400mg (8-50mg capsules) orally twice daily until disease
progression

Application Type/Number: NDA 206162

Applicant/sponsor: Astra-Zeneca

OSE RCM #: 2014-341

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1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) olaparib. Astra-Zeneca submitted a New Drug Application (NDA 206162) for olaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA mutation as detected by an FDA-approved test, who are in response (complete response or partial response) to platinum-based chemotherapy. This indication was amended on July 24, 2014 to: monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The sponsor did not submit a proposed REMS, but submitted a Risk Management Plan, in which it proposes to manage adverse events in labeling with routine pharmacovigilance.

1.1 BACKGROUND

Ovarian cancer is the fifth cause of cancer related deaths among women, and accounts for more deaths than any other cancer of the reproductive system. The American Cancer Society estimates 21,980 women will be diagnosed with ovarian cancer, and 14,270 will die from this disease.¹ The risk of developing ovarian and breast cancer is increased if a deleterious mutation in the BRCA1 or BRCA2 gene is present. It is estimated that the incidence of deleterious germline BRCA mutation (gBRCAm)-associated ovarian cancer is approximately 10-15% of cases of ovarian cancer, corresponding to an annual incidence of approximately 2,000 cases per year in the U.S.² Although the risk of developing ovarian cancer is increased with the deleterious gBRCAm, its presence appears to be correlated with increased susceptibility to chemotherapy as well as increased survival.² The current standard of care for treatment of advanced ovarian cancer may include a combination of surgical debulking and chemotherapeutic regimens consisting of a platinum agent such as carboplatin or cisplatin, with a taxane such as paclitaxel or docetaxel. Other chemotherapeutic agents used in this setting may also include gemcitabine, pegylated liposomal doxorubicin, and topotecan.² Adverse events such as myelosuppression, gastrointestinal effects, neurotoxicities, and hypersensitivity reactions can be severe, and greatly impact patient quality of life.

Patients with gBRCAm-associated ovarian cancer may be exposed to multiple courses of various chemotherapeutic regimens due to increased susceptibility of these agents in this setting. Patients who initially respond to platinum-based chemotherapy and who subsequently relapse six months or more after their initial treatment are classified as “platinum sensitive,” and most will respond to successive platinum-based chemotherapy with response rates ranging from 30%-90%.³ The likelihood of clinical benefit or

¹ www.cancer.org/cancer/ovariancancer/detailedguide/ovarian-cancer-key-statistics

² FDA ODAC Briefing Document, Olaparib NDA 206162, June 25, 2014

³ Davis A et al. Platinum resistant ovarian cancer: What is it, who to treat and how to measure benefit? *Gynecologic Oncology* (2014), <http://dx.doi.org/10.1016/j.ygyno.2014.02.038>

response to second-line platinum based chemotherapy correlates with the length of time interval between primary chemotherapy and relapse. Patient response rates and the duration of treatment response declines with each subsequent chemotherapeutic regimen.³ Treatment-free intervals are of significant value in the quality of life in this patient population to experience recovery time from multiple adverse reactions of chemotherapy prior to the next inevitable treatment regimen.²

Olaparib: Olaparib is a first in class oral PARP inhibitor designed to exploit deficiencies in DNA pathways of BRCA mutated cancer cells resulting in cancerous cell death. Inhibition of the PARP enzyme, which is involved in the base excision DNA repair pathway, results in lack of DNA repair and cell death in homologous recombination (HR) pathways found in BRCA-mutated cells.⁴ The proposed dose is 400 mg (8-50 mg capsules) twice daily as monotherapy in patients with deleterious or suspected deleterious gBRCAm (as detected by an FDA approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. In addition, the Sponsor is seeking co-approval of a companion diagnostic test with Myriad Pharmaceuticals for detection of BRCA mutations in this patient population.

1.2 REGULATORY HISTORY

The review classification this application is Priority, and is undergoing accelerated approval. Pertinent regulatory history dates are noted below:

- IND 75918 activated – August 22, 2006
- Guidance Meeting – October 23, 2012
 - The olaparib development program for patients with gBRCAm associated ovarian cancer was discussed. FDA considered the gBRCAm subgroup results of Study 19 to be promising, yet insufficient to support approval.
- Pre-submission Meeting – March 18, 2013
 - Joint meeting with FDA/CDER/CDRH, AstraZeneca, and Myriad Genetics Inc. to discuss the regulatory pathway for approval of the companion diagnostic assay
- Breakthrough Therapy Designation requested on the basis of Study 19 – March 19, 2013
- Breakthrough Therapy Designation denied – May 16, 2013
- Pre-NDA meeting – October 2, 2013
 - FDA stated its expectation for a potential concurrent NDA and PMA approval and the likelihood that the application would be discussed at an advisory committee. Discussions whether a REMS would be necessary for the submission of an NDA was not discussed at this meeting.
- Orphan drug status granted October 16th, 2013
- NDA 206162 submitted for olaparib – February 3, 2014
 - Proposed indication with this submission: “monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed

⁴ Liu JF, et al, PARP inhibitors in ovarian cancer: Current status and future promise, Gynecol Onco (2014), <http://dx.doi.org/10.1016/j.ygyno.2014.02.039>

ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA mutation as detected by an FDA-approved test who are in response (complete response or partial response) to platinum-based chemotherapy.”

- Oncologic Drug Advisory Committee June 25th, 2014
 - The Division of Oncology Products 1 (DOP-1) sought advice from the committee on the following:
 - Voting Question: Do the efficacy results from Study 19, specifically a seven-month improvement in median progression-free survival (PFS) and a hazard ratio of 0.17, along with the safety data in the gBRCAm population, demonstrate a favorable risk-benefit profile of olaparib maintenance monotherapy in gBRCAm-associated, platinum-sensitive, relapsed high-grade serous ovarian cancer that is in response to platinum-based chemotherapy?
 - What is the appropriate magnitude of treatment effect for median improvement and hazard ratio to be demonstrated in the confirmatory SOLO-2 trial to consider olaparib to be of direct clinical benefit to this patient population.
 - Vote Result: No – 11, Yes – 2, Abstain – 0. Those that voted no cited several concerns with the existing data of Study 19, the Sponsor’s registrational study, as well as a preference for improvement in overall survival versus progression free survival in the Sponsor’s proposed setting of using olaparib as maintenance therapy. Members who voted no also discussed concerns with the occurrence and duration of adverse effects such as severe fatigue and gastrointestinal toxicities, as well as occurrences of secondary cancers in a maintenance setting where patients would otherwise not receive drug therapy, and hence, not experience any adverse events.
 - In regards to the second question, many of the committee members described a strong preference for use of overall survival as the primary endpoint for trials in this patient population, however, most committee members were unable to state a specific magnitude of effect that would demonstrate a favorable risk-benefit profile for the Sponsor’s confirmatory study in this patient population.
- Major amendment – July 24th, 2014
 - The indication for olaparib was narrowed and defined as monotherapy (versus maintenance therapy) in patients with deleterious or suspected deleterious gBRCAm (as detected by an FDA approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. This required the Sponsor to send in data specific to this patient population.
- New PDUFA date based on major amendment: January 2, 2015

2 MATERIALS REVIEWED

- Olaparib Pre-NDA Meeting minutes – October 7, 2013
- Olaparib Application Orientation meeting – March 28, 2014:
- Olaparib Clinical Overview (section 2.5), Clinical Safety (section 2.74), Nonclinical Overview (section 2.4).
- Olaparib Midcycle Communication Slides – May 6, 2014
- Olaparib Oncologic Drug Advisory Committee FDA Briefing Document – June 25, 2014
- Summary of Minutes of the Oncologic Drugs Advisory Committee Meeting for Olaparib – July 16, 2014
- Draft Olaparib (Lynparza) label (near final), November 17, 2014

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Olaparib 400 mg twice daily as monotherapy has been studied in 300 patients with gBRCAm advanced ovarian cancer, and 223 of these patients have received three or more prior lines of chemotherapy.⁵ Included in the 223 patients who have received three or more prior lines of chemotherapy, 137 have deleterious or suspected deleterious gBRCAm advanced ovarian cancer.

Key Efficacy Findings⁵ - The efficacy of olaparib was investigated in a single-arm study of 137 patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer who were treated with three or more lines of prior chemotherapy (Study 1). Treatment was 400 mg twice daily as monotherapy until disease progression or intolerable toxicity. Ninety-four percent of the study population was Caucasian with a median age of 58 years. Deleterious or suspected deleterious gBRCAm status was verified retrospectively by an FDA approved test, BRCA*Analysis* CDx™. Objective Response Rates (ORR) and duration of response (DOR) were assessed by the investigator according to RECIST v1.1.4 criteria. Efficacy results from Study 1 are summarized below:

Overall Response and Duration of Response in Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy⁶

	N=137
Objective Response Rate (95% CI)	34% (26, 42)
Complete Response	2%
Partial Response	32%
Median DOR in months (95% CI)	7.9 (5.6, 9.6)

⁵ Olaparib(Lynparza) near final draft label, November 10, 2014

⁶ Efficacy Results from Study 1, Table 5 – Olaparib (Lynparza) near final draft label, November 10, 2014

3.2 SAFETY CONCERNS⁵

The safety of olaparib was evaluated in 223 patients who have received three or more prior lines of chemotherapy, which includes 137 patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer. Adverse reactions reported in 20% or more of patients include: anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dyspepsia, headache, decreased appetite, nasopharyngitis/URI, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash, and (b) (4) abdominal pain. Laboratory abnormalities reported in 25% or more of patients include: increase in creatinine, mean corpuscular volume elevation, and myelosuppression (specifically decreases in hemoglobin, lymphocytes, absolute neutrophil count, and platelets). Adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%. Of note, pneumonitis, embryo-fetal toxicity, and Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) are adverse events that will be highlighted in Warnings and Precautions. Fatal cases of pneumonitis occurred in <1% of patients treated with olaparib. Due to the mechanism of action of olaparib, and based on findings in nonclinical data, olaparib is found to be teratogenic in exposures below the recommended dose of 400 mg twice daily. Olaparib will be labeled as Pregnancy Category D.

MDS/AML was an adverse event that both FDA clinical reviewers and the Sponsor highlighted in the Advisory Committee briefing packet. A summary of these events reported in the olaparib clinical trial program analyzed by the FDA is noted below.

- **Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML):** MDS/AML have been confirmed in 6 out of 298 (2%) of patients enrolled in a single arm trial of olaparib monotherapy, in patients with deleterious or suspected deleterious germline *BRCA*-mutated (gBRCAm) advanced cancers.⁵ In a randomized placebo controlled trial, MDS/AML occurred in 3 out of 136 (2%) patients with advanced ovarian cancer treated with olaparib.⁵ In the overall clinical development program, MDS/AML were reported in 22 of 2,618 (<1%) patients treated with olaparib, and of these cases, 17/22 were fatal. The duration of olaparib treatment in these patients ranged from less than 6 months to more than 2 years, and all patients received previous chemotherapy with other DNA damaging agents. Further evaluation of MDS/AML will involve a post-marketing requirement (see Section 4 of this review).

Deaths - There were 8 (4%) patients with adverse reactions leading to death. Two were attributed to acute leukemia, and one each was attributed to COPD, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture.

The sponsor did not submit a REMS to manage any adverse reactions, but did submit a risk management plan which proposed to include the adverse events in labeling and in routine pharmacovigilance.

4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

The following post-marketing requirements have been negotiated with the Sponsor:

- Submit the results of the ongoing randomized double-blind, placebo-controlled, multi-center trial to assess the efficacy of olaparib maintenance monotherapy in

relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)) who have responded following platinum based chemotherapy (Study D0818C00002, SOLO-2).

- Conduct and submit the results of a randomized trial establishing the superiority of olaparib over physician’s choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline *BRCA1/2* mutations (Study D0816C00010).
- Provide annual summaries of all cases of Acute Myelogenous Leukemia / Myelodysplastic Syndrome identified in patients treated with Lynparza (olaparib). These reports should summarize all cases identified up until that reporting date (new cases and those reported in previous years), and should include patients treated with Lynparza on clinical trials and outside of clinical trials (including spontaneous safety reports).
- Submit the final report for trial D0816C00006 entitled, “An Open-label, Non-randomized, Multicenter, Comparative, and Phase I Study of the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Renal Function or Renal Impairment”.
- Submit the final report for trial D0816C00005 entitled, “An Open-label, Non-randomized, Multicenter, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Hepatic Function or Mild or Moderate Hepatic Impairment.”

5 DISCUSSION

When evaluating factors of whether a REMS is necessary to ensure that the benefit outweighs the risks for olaparib, considerations such as patient population, the seriousness of known or potential adverse events, and prescribing population strengthen the support of the appropriateness to manage the risks of this drug within professional labeling.

The estimated population of women with deleterious gBRCAm-associated ovarian cancer is approximately 10-15% of cases of ovarian cancer, corresponding to an annual incidence of approximately 2,000 cases per year in the U.S. Based on feedback from the Advisory Committee, and through further analysis of the data from FDA clinical reviewers, the original indication submitted with the application was changed from a broader indication that proposed *maintenance* therapy in patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with gBRCAm (as detected by an FDA approved test) who are in response (complete response or partial

response) to platinum-based chemotherapy, to monotherapy in patients with deleterious or suspected deleterious gBRCAm (as detected by an FDA approved test) advanced ovarian cancer who have received 3 or more prior lines of chemotherapy. This indication narrows the patient population further, by making olaparib nearing the last line of treatment. Patients diagnosed with platinum sensitive relapsed ovarian cancer have dismal outcomes; with five year survival rates of 27% in patients with advanced disease. Despite the presence of the gBRCAm to be correlated with increased susceptibility to chemotherapy and survival, each subsequent regimen shortens the time to progression, and patients will ultimately die from this disease. In the single arm trial of 137 patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer, 34% had objective response rates, of which 32% had a partial response, and 2% had a complete response. The median duration of response seen in these patients was approximately eight months.

Olaparib is a new molecular entity, and if approved, will be the first in class PARP inhibitor for the treatment of gBRCAm advanced ovarian cancer. Although there are currently no other FDA approved PARP inhibitors to compare the benefit:risk profile, adverse events associated with olaparib in the clinical trial program are similar to those seen in clinical practice with other chemotherapies such as anemia, gastrointestinal events, rash, and arthralgia. Adverse events highlighted in Warnings and Precautions will include MDS/AML, pneumonitis, and embryo-fetal toxicity. MDS/AML were reported in 22 of 2,618 (<1%) in overall patients treated with olaparib, and of these cases, 17/22 were fatal. Therapy-related AML is a rare and fatal complication of cytotoxic chemotherapy, often preceded by the development of secondary MDS. The development of MDS/AML in recurrent ovarian cancer has been linked with the use of other DNA damaging chemotherapies such as alkylating agents and platinum-based chemotherapies.⁷ The rate of MDS in the general population according to data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (Seer) program is approximately 3.3 per 100,000, however, this number is thought to underestimate the true incidence of MDS due to under-reporting.⁸ FDA reviewers note that the reported incidence of MDS/AML in the olaparib database is higher than the expected incidence in the general population and in an ovarian cancer population treated with prior platinum-based therapies.² However, because there is concern that MDS/AML may be under-reported, and all patients who received olaparib also received previous chemotherapy with other DNA damaging agents, this is a safety signal that warrants further investigation as a post-marketing requirement that may provide a better characterization of this risk.

Olaparib will be primarily, if not exclusively, prescribed by oncologists who are familiar with the management of chemotherapeutic toxicities such as myelosuppression, gastrointestinal effects, and various respiratory adverse events. Fatal cases of pulmonary toxicity and respiratory failure is labeled for gemcitabine, and interstitial lung disease (including fatalities) is labeled for topotecan.^{9,10} The risk of pneumonitis (including fatal

⁷ Olaparib Summary of Clinical Safety, Section 2.4

⁸ Cogle C.R., et al. Incidence of the Myelodysplastic syndromes using a novel claims-based algorithm: high number of uncaptured cases by cancer registries. 2011 *Blood*; 117(26):7121-5.

⁹ Gemzar US Prescribing Information

cases) with olaparib will be addressed in Warnings and Precautions similar to other drugs used in the treatment of ovarian cancer. All chemotherapies used in ovarian cancer have non-clinical data that evidence the teratogenic potential of these agents, and are labeled as Pregnancy Category D. Nonclinical data for olaparib also show that it has teratogenic potential, however, the median age of women in the olaparib trials was post-menopausal (58 years). Olaparib will also be labeled as Pregnancy Category D like other chemotherapies for the treatment of ovarian cancer. Since these risks are not uncommon or unknown to this prescribing population, these risks can be communicated through professional labeling.

6 CONCLUSION

DRISK concurs with the Division of Oncology Products-1 that if approved, under accelerated approval based on objective response rate and duration of response, a REMS is not necessary to ensure the benefits of olaparib outweigh the risks in patients with deleterious or suspected deleterious gBRCAm (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit risk profile to be re-evaluated.

¹⁰ Topotecan US Prescribing Information

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/s/

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