

## Summary Review for Regulatory Action

<b>Date</b>	12/16/2014
<b>From</b>	Amna Ibrahim MD
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	206162
<b>Applicant Name</b>	ASTRAZENECA PHARMACEUTICALS LP
<b>Date of Submission</b>	02/03/2014
<b>PDUFA Goal Date</b>	01/03/2015
<b>Proprietary Name / Established (USAN) Name</b>	Lynparza olaparib
<b>Dosage Forms / Strength</b>	Capsule/ 50 mg per capsule
<b>Proposed Indication(s)</b>	As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA (gBRCA) mutation as detected by an FDA-approved test who are in response (complete response or partial response) to platinum-based chemotherapy.
<b>Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Kim, Geoffrey (efficacy)/Ison, Gwynn (safety)
Statistical Review	Zhang, Hui
Pharmacology Toxicology Review	Ricks, Tiffany/ Haw-Jyh Chiu
CMC Review/OBP Review	Russell, Anne Marie/ Ladouceur, Gaetan
Clinical Pharmacology Review	Pfuma, Elimika
DDMAC	Toscano, Marybeth
OSI	Iacono-Connors, Lauren C
CDTL Review	McKee, Amy
OSE/DMEPA	Mathew, Davis
OSE/DRISK	Naomi Redd,
QT-IRT	Rekic, Dinko
DMPP	Walker, Morgan
OSI	Iacono-Connors, Lauren

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

OSI= Office of Scientific Investigations

DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader

Division of Medical Policy Programs (DMPP)

## 1. Introduction

NDA 206162 for the New Molecular Entity (NME), olaparib, was originally submitted for the following indication as proposed by the applicant.

“as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA (gBRCA) mutation as detected by an FDA-approved test who are in response (complete response or partial response) to platinum-based chemotherapy.”

A single randomized, placebo-controlled study (study 19) was submitted to support the above maintenance indication. The applicant requested a priority review which was granted. This application was discussed at an ODAC meeting on June 25, 2014 where a delay in approval of olaparib was recommended by an 11-2 vote. See section 9 for a brief discussion on the ODAC proceeding.

After the ODAC and within this review cycle, the applicant submitted results and datasets to support an indication in a non-maintenance setting in heavily-pretreated patients with BRCA-positive ovarian cancer after discussions with the FDA (see section 7 and 8). The risk-benefit assessment is considered favorable for this population. The indication recommended for an accelerated approval in the non-maintenance setting is:

“as 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.”

A companion diagnostic assay has been submitted by Myriad Genetics Inc. to support a Premarket Approval application (PMA) for use in patient selection for this indication.

## 2. Background

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. Previously, in 2013, a (b) (4) request was denied (b) (4) of olaparib as maintenance treatment in patients with germline BRCA-mutated (gBRCAm) ovarian cancer. After the unfavorable vote from ODAC, the applicant submitted additional data to support the NDA.

The accelerated approval of olaparib is recommended based on the results of a single-arm study in patients with deleterious or suspected deleterious gBRCAm advanced cancers which demonstrated a durable 34% response rate. The placebo-controlled randomized trial of olaparib as maintenance therapy provided additional safety information. Two randomized trials have been identified to serve as potential confirmatory trials and will serve as PMRs. See section 13.

As per Dr McKee, the capsule formulation reviewed in this application is no longer being used in clinical development. The applicant has changed the formulation to a tablet that has higher

bioavailability than the current capsule formulation. Dr McKee states that ultimately, the efficacy and safety of the new formulation is being tested in current and future clinical trials that are the subject of post-marketing requirements. (b) (4)

### 3. CMC/Device

CMC Drug Product reviewer, Anne Marie Russell PhD, and Drug Substance reviewer, Gaetan Ladouceur, PhD, recommended approval from a Chemistry, Manufacturing and Controls standpoint.

Dr Russell states in her review that based on the stability results and analysis of clinical capsule (b) (4), the recommended expiry for the olaparib drug product is eighteen months under long term conditions of 25°C. The applicant agreed, in a Post Marketing Commitment, to conduct repeat ICH primary stability studies for three validation batches. An annual commercial batch will be placed on stability according to the submitted post-approval stability protocol, provided production warrants.

A concern regarding thermal failure of capsule at higher temperatures was noted. According to Dr Russell, appearance testing reports thermal failure at (b) (4) for batches 3063386R, 3114165R and 3115337R. The appearance test results report “capsules showed evidence of leakage”, “capsule shell has deformed” and “capsule shell has deformed and printing ink smudged suggesting leakage of capsule content” respectively. The labeling was amended to mitigate issues arising from exposure of capsules to high temperatures. In section 2.2 (Recommended Dosing), it is stated that “do not take capsules which appear deformed or show evidence of leakage”. In addition, it is stated in section 16.2 (Storage) that, “Lynparza should not be exposed to temperatures greater than 40°C or 104°F. Do not take Lynparza if it is suspected of having been exposed to temperatures greater than 40°C or 104°F.”

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of eighteen months. There are no outstanding issues.

### 4. Nonclinical Pharmacology/Toxicology

Tiffany Ricks PhD and Haw-Jyh Chiu PhD recommended approval of the NDA. Secondary and tertiary reviewers Todd Palmby PhD and John Leighton PhD also recommended approval.

Dr Palmby in his review discusses the mechanism of action of olaparib and correlation of the toxicities in non-clinical studies with those observed in patients. Per Dr Palmby, olaparib’s mechanism of action involves an interaction with the enzymatic repair machinery that carries out SSB detection and repair. He stated that the Applicant’s rationale for conducting clinical trials that supported this NDA submission was that combining the activity of olaparib with a deficiency in the double-strand DNA break (DSB) repair pathway, such as mutations in BRCA, may lead to an enhanced accumulation of double-strand DNA breaks, eventually leading to tumor cell death. Olaparib’s mechanism of action is consistent with the

clastogenicity observed in genetic toxicology studies, and has the potential to translate into an increased risk of developing secondary malignancies in patients treated with Lynparza. This risk may be further increased in patients with deleterious or suspected-deleterious mutations in BRCA. Olaparib's anti-tumor activity and its potential activity to induce secondary malignancies may be through the same mechanism. Cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) were reported in patients treated with olaparib in clinical trials.

Dr Palmby also noted in his review that per CMC reviewers, the proposed NMT <sup>(b) (4)</sup>% acceptance criteria for the content of the degradant, <sup>(b) (4)</sup>, in olaparib capsules at end of expiry was not qualified. At FDA's behest, drug product specifications were to be revised including an acceptance criterion for <sup>(b) (4)</sup> of <sup>(b) (4)</sup>%.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

## 5. Clinical Pharmacology/Biopharmaceutics

Elimika Pfuma, PhD, states in her review that the Office of Clinical Pharmacology (Division of Clinical Pharmacology V and Division of Pharmacometrics) has reviewed the information contained in NDA 206162. This NDA is acceptable from a clinical pharmacology perspective.

Dr Pfuma stated in her review that Olaparib exposure increases with dose in the range valuated (up to 600 mg). Limited data suggest that the systemic exposure (AUC) of olaparib increases less than proportionally with dose over the dose range of 100 to 400 mg, but the PK data were variable across trials. A high-fat meal did not increase the exposure of olaparib significantly; therefore olaparib can be dosed without regard to food. The mean half-life is 12 hours at the 400 mg dose. Dedicated hepatic and renal impairment trials are currently ongoing. The results of the hepatic and renal impairment studies will be submitted as PMRs.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical-Efficacy

Per the primary clinical review, Study 42 was a single-arm, open-label, multicenter study assessing the response rate of olaparib in patients with advanced cancers who have a deleterious gBRCA mutation. Initially, up to 150 patients with known gBRCA status were to be recruited; however, after protocol amendments, this number was increased to 300 patients, with the intention that 220 patients with either breast or ovarian cancer would be enrolled with the other patients having prostate, pancreatic, or other tumor types associated with gBRCA deficiencies.

Of the 193 patients with ovarian cancer on this trial, 137 patients with measurable, *gBRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy who were enrolled to this trial were assessed. Carboplatin was received by all but 1 patient, and 46 had previously received cisplatin. A majority of patients had also received paclitaxel, doxorubicin and gemcitabine. All patients received olaparib at a dose of 400 mg twice daily as monotherapy until disease progression or intolerable toxicity. Objective response rate and duration of response were assessed by the investigator according to RECIST v1.1. The efficacy results are summarized below.

**Table: Overall Response and Duration of Response in Patients with *gBRCA*-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42**

	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)

From the label

A pooled population of patients with *gBRCA*m-associated ovarian cancer, with measurable disease, who had received three or more prior lines of chemotherapy, had results consistent with that of study. These patients were treated with olaparib using the same dose and regimen.

Hui Zhang, PhD, in her biostatistics review stated that the trial 42 was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed. Whether the data and analyses from the current submission demonstrated an overall favorable benefit versus risk profile is deferred to the clinical team reviewing this application.

## 8. Safety

As per the label, olaparib 400 mg twice daily as monotherapy has been studied in 300 patients with *gBRCA*-mutated advanced ovarian cancer, and 223 of these patients had received 3 or more prior lines of chemotherapy. In the 223 patients with *gBRCA*-mutated ovarian cancer who received 3 or more prior lines of chemotherapy, adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%. 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.

According to the label, the most common adverse reactions ( $\geq 20\%$ ) in clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/pharyngitis/URI, cough,

arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash and abdominal pain/discomfort. The most common laboratory abnormalities ( $\geq 25\%$ ) were increase in creatinine, mean corpuscular volume elevation, decrease in hemoglobin, decrease in lymphocytes, decrease in absolute neutrophil count, and decrease in platelets.

Myelodysplastic syndrome/Acute Myeloid Leukemia, pneumonitis and embryo-fetal toxicity are included in Warning and Precautions. The incidence of myelodysplastic syndrome was approximately 2% in 298 patients advanced cancers with deleterious or suspected deleterious *gBRCAm* mutation and in 136 patients with advanced ovarian cancer treated with olaparib in a randomized placebo controlled trial. Per the primary safety review, “the majority of the patients who developed MDS/ AML in this database (17 of 22 patients) have died. It is important to consider the MDS/AML incidence from the olaparib database in the context of the overall annual incidence of MDS/AML in the US. There is an estimated annual incidence of MDS in the US of approximately 3.3 cases per 100,000, or 0.0033%. The incidence in a large case-control study of almost 29,000 ovarian cancer patients who had received prior platinum therapy, was 0.3%. The incidence of MDS and AML in a population of patients carrying a *gBRCA* mutation is unknown. However, the incidence in Study 19 (maintenance study) was markedly higher than these reported figures, at 2.2%. Likewise, the incidence out of the 193 ovarian cancer patients treated in Study 42 (single arm study) was 3.1%. And the incidence in the entire safety database is also notable, in comparison, at 0.8%. Based upon these figures, the risk of treating patients with olaparib needs to be weighed against the potential benefit a given patient may expect to gain from this therapy.” This toxicity will be evaluated as a Postmarketing Requirement (PMR). See section 13.

As included in the label, pneumonitis, including fatal cases, occurred in  $<1\%$  of patients treated with olaparib. Per the safety review, “the adverse event of pneumonitis in the context of olaparib therapy is rare; however, five of the ten cases (50%) reported had a fatal outcome. Therefore, this event has serious potential consequences for patients.” Based on its mechanism of action and findings in animals, olaparib can cause fetal harm when administered to a pregnant woman.

## 9. Advisory Committee Meeting

The following excerpt from Dr McKee’s CDTL review captures the major points from the ODAC.

The Oncologic Drugs Advisory Committee (ODAC) met June 25, 2014, to discuss NDA 206162. The ODAC was presented data and discussion for the indication in the platinum-sensitive maintenance setting, which was supported primarily by Study 19. The key issues raised by the FDA review team included loss of randomization for *gBRCAm* subgroup; estimation of the treatment effect of olaparib therapy; risks of olaparib therapy in the platinum-sensitive maintenance setting, including the risk of MDS/AML; and the reproducibility of results in a larger trial with a pre-planned analysis for this *gBRCAm* subgroup.

The first question posed to the Committee was the following:

- Do the safety and efficacy results from Study 19 in the *gBRCAm* population support an accelerated approval, or should marketing approval consideration be delayed until the results from SOLO-2 are available?

There were 11 No votes as compared to 2 Yes votes. As justification for voting against approval for olaparib at this time, committee members cited the lack of an overall survival benefit for maintenance therapy; the unreliability of the results due to loss of randomization and small sample size; the toxicity of therapy and risk of MDS/AML for patients not otherwise undergoing treatment; and the potential to hinder accrual to confirmatory study.

Please refer to the primary review and ODAC transcript for greater details.

## **10. Pediatrics**

A waiver from conducting pediatric studies was granted for this indication.

## **11. Other Relevant Regulatory Issues**

- **OSI Audits:** As per the clinical review, the Office of Scientific Integrity (OSI) conducted clinical inspections of four clinical sites and the applicant. These sites were that of Dr. Phillip Harter (Germany), Dr. Charlie Gourley (UK), and two sites of Dr. Ursula Matulonis (Boston, USA). These sites were chosen due to relatively high enrollment numbers to Study 19 and were inspected with primary regards toward the conduct of Study 19. The sites of Dr. Matulonis and Dr. Gourley also enrolled patients onto Study 12. Dr. Gourley's site also enrolled patients onto studies 2 and 24. After the major amendment was submitted to the NDA, the decision was made to not pursue additional clinical site inspections as there were no major conduct deficiencies at the inspected clinical sites and it is reasonable to assume that the study site conduct would not be drastically different for the other studies whose data are used to support the revised indication. In addition, a large portion of data in support of the revised indication comes from Israel. At the time of the submission of the major amendment, the State Department issued a travel warning to US citizens recommending the deferral of non-essential travel to Israel. Sending an inspection team to Israel at that time did not appear to be an appropriate use of FDA resources especially considering that no major deficiencies were identified at the clinical sites and the applicant.
- **Financial Disclosure:** As per the primary clinical review, disclosures of financial interests were submitted for 3 sub-investigators. The reviewer commented that the financial interests of the sub-investigators identified have a very low likelihood of affecting the outcomes of the study due to small numbers of patients enrolled at each respective site. These investigators enrolled patients on studies 12, 19 and 20.

There are no other unresolved relevant regulatory issues.

## 12. Labeling

Includes:

- Proprietary name: The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. Per Matthew Davis, Pharm D, DMEPA reviewer, the proposed proprietary name is acceptable from both a promotional and safety perspective.
- Physician labeling: all labeling issues were resolved during labeling meetings
- Carton and immediate container labels are acceptable
- Patient labeling/Medication guide: The Medication Guide was reviewed by the DMPP (Division of Medical Policy Programs) Patient Labeling Review team. The recommendations were discussed and incorporated in labeling meetings.

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action:  
I recommend an accelerated approval for this NDA.
- Risk Benefit Assessment

As per the primary clinical review, “the observed response rate of 34% in the patients with gBRCAm-associated ovarian cancer who have received three lines of chemotherapy is better than what would be expected of available therapy and represents an improvement on a surrogate endpoint that is reasonably likely to predict clinical benefit.”

A durable response rate is an established endpoint in heavily pre-treated cancer patients as it is able to isolate the antitumor effect. The serious risk of MDS/AML is considered acceptable considering the poor therapeutic options available to this population. This risk is mitigated by the use of this drug in selected patients (with gBRCA mutation) who based on the mechanism of action are more likely to respond to olaparib. Confirmation of clinical benefit will be required as part of accelerated approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

There will be 5 PMRs and 1 PMC for this NDA.

- a) Two of these are related to accelerated approval and consist of two randomized clinical trials in patients with BRCA-positive ovarian cancer. Progression-Free Survival and

Overall Survival analyses from these studies in the maintenance setting and platinum-sensitive relapse will be submitted to verify and confirm clinical benefit. These PMRs are as follows:

Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial D0818C00002, SOLO-2, 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.

Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial D0816C00010, 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.

- b) For the 3rd PMR, the applicant will collect and analyze all cases of MDS/AML and submit a report on an annual basis for 5 years to provide a more accurate assessment and understanding of the risk for this condition. This PMR is as follows:

Collect and analyze all cases of acute myelogenous leukemia/ myelodysplastic syndrome identified in patients treated with Lynparza (olaparib) on an annual basis. These interim 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) to provide an accurate assessment of the long-term incidence and risk of AML/MDS

- c) Postmarketing Requirements also include two organ impairment trials. These PMRs are as follows:

Submit the final report for trial D0816C00006 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, and Phase 1 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 1 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."

- d) The applicant agreed to a Postmarketing Commitment to conduct repeat ICH primary stability studies for three validation batches.

Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry.

Amna Ibrahim MD  
Acting Director  
DOP1

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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AMNA IBRAHIM  
12/16/2014