CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s000

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208558

Application Type: New NDA

Drug Name(s)/Dosage Form(s): LYNPARZA™ (olaparib) Tablets/100 mg, 150 mg

Applicant: AstraZeneca Pharmaceuticals LP

Receipt Date: February 22, 2017

Goal Date: August 22, 2017

1. Regulatory History and Applicant's Main Proposals

NDA 206162 was approved on December 19, 2014, for Lynparza™ (olaparib) capsules and indicated as monotherapy for 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. This application is for a new tablet formulation of olaparib, and is being submitted as a separate NDA from the approved capsule formulation. Clinical and nonclinical studies that supported the capsule approval also support the tablet formulation.

Two pivotal studies support the requested indication for maintenance treatment of patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (complete response or partial response) to platinum based chemotherapy. The indication being sought is for a population that is selected on the basis of response to platinum therapy and as such, no diagnostic assay is required.

This application also requests that the indication awarded to the capsules in NDA 206162 (treatment of 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) be conferred to the tablet formulation of olaparib.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment: *Subsections 1.1, 1.2, 2.3, 7.2, 7.3 and 14.2 are not in title case.*

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Subsection headings are not in title case for subsections 1.1, 1.2, 2.3, 7.2, 7.3 and 14.2.*

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
08/15/2017

CHRISTY L COTTRELL
08/16/2017

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #	208558
Product Name:	Lynparza (Olaparib) 150 mg tablet, 100 mg tablet
PMC Description: 3238-1	Submit the progression-free survival (PFS) and molecular characteristics (patient and tumor) final report, labeling, and datasets from clinical trial D0816C00020, entitled, "OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non- Germline BRCA mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy."

PMR/PMC Schedule Milestones:

Draft Protocol Submission:	08/2017
Final Protocol Submission	11/2017
Trial Completion:	12/2020
Final Report Submission:	06/2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Olaparib is being approved for all women with recurrent ovarian cancer that is in response (complete or partial) to platinum-based treatment. The safety and efficacy of olaparib for maintenance in the population with germline *BRCA* mutation has been established in the SOLO2 trial. The safety and efficacy of maintenance in an all-comer population was established by the Study 19 trial, which included a large number of g*BRCA*m patients; these patients have a serious and life-threatening condition with an unmet need for better therapies. The magnitude of olaparib benefit in the maintenance setting in women with BRCA-negative tumors (germline and somatic) and with the presence or absence of homologous recombination deficient markers remains uncertain.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

OPINION is a planned, multicenter, nonrandomized study of olaparib in patients with germline wildtype BRCA platinum-sensitive relapsed ovarian cancer. This trial will further establish the magnitude of effect in the maintenance setting for olaparib in patients without germline BRCA mutation, including patients without somatic BRCA mutation, and with and without HRD tumors.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Multicenter, open-label, single-arm trial to assess the safety and efficacy of single-agent olaparib as a maintenance treatment in patients with germline BRCA wildtype ovarian cancer (trial D0816C00020, entitled OPINION).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #	208558
Product Name:	Lynparza (Olaparib) 150 mg tablet, 100 mg tablet
PMC Description: 3238-2	Submit the overall response rate (ORR) and duration of response (DOR) analyses with datasets from clinical trial D0816C00010: (SOLO3), entitled " 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."

PMR/PMC Schedule Milestones:

Draft Protocol (Amendment) Submission:	10/2017
Draft Statistical Analysis Plan Submission:	11/2017
Final Protocol Submission	12/2017
Trial Completion	02/2019
Final Report Submission	08/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Olaparib is being approved for women with recurrent ovarian cancer that is incomplete or partial response to platinum-based treatment as SOLO2 and Study 19 have verified the clinical benefit of olaparib in this earlier line setting. As a result, the accelerated approval of olaparib in the fourth-line treatment setting for women with germline BRCA mutation will be converted to regular approval with this application.

However, the Agency affirms that SOLO3 represents a critical trial and would provide valuable information regarding the utility of olaparib in the 3rd-line setting. The Agency recommends that the applicant continue SOLO3. We will plan to release the PMR 2824-2 and reissue PMC 3238-X.

(b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See rationale in #1

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized study establishing the superiority of olaparib over physician's choice single agent chemotherapy for the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline *BRCA1/2* mutations (Study D0816C00010), with primary endpoints including objective response rate and duration of response.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)

☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #	208558
Product Name:	Lynparza (Olaparib) 150 mg tablet, 100 mg tablet
PMC Description: 3238-3	Submit the 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.

PMR/PMC Schedule Milestones:

Trial Completion:	06/2019
Final Report Submission:	12/2019

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

Olaparib is receiving regular approved for all women with recurrent ovarian cancer that is in response (complete or partial) to platinum-based treatment. The safety and efficacy of olaparib for maintenance in the population with germline *BRCA* mutation has been established using the PFS the SOLO2 trial. The safety and efficacy of maintenance in an all-comer population was established by the Study 19 trial, which included a large number of g*BRCA*m patients; these patients have a serious and life-threatening condition with an unmet need for better therapies. The magnitude of olaparib survival benefit in the maintenance setting in women with germline BRCA-mutated tumors (germline and somatic) remains uncertain.

7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

SOLO2 is an ongoing, multicenter, randomized trial of olaparib versus placebo in women with relapsed, germline BRCA-mutated ovarian cancer, using olaparib as maintenance therapy following complete or partial response to platinum-based chemotherapy. The OS results will further elucidate the survival benefit of maintenance treatment with olaparib for women with platinum-sensitive relapsed ovarian cancer.

8. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Ongoing multicenter, open-label, randomized, placebo-controlled trial to assess the safety, efficacy, and overall survival benefit of single-agent olaparib as a maintenance treatment in patients with platinum-sensitive, relapsed, germline BRCA-mutated ovarian cancer (SOLO2).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

10. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHRISTINA D MARSHALL
08/15/2017

KATHERINE M FEDENKO
08/15/2017

Clinical Inspection Summary

Date	July 19, 2017
From	Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation
To	Rajesh Venugopal, Regulatory Project Manager Gwynn Ison, Clinical Reviewer Division of Oncology Products 1
NDA #	208558
Applicant	AstraZeneca Pharmaceuticals LP
Drug	Lynparza (Olaparib)
NME	No
Therapeutic Classification	Priority
Proposed Indication	Ovarian Cancer
Consultation Request Date	March 21, 2017
Summary Goal Date	July 21, 2017
Action Goal Date	August 22, 2017
PDUFA Date	August 22, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study D0816C00002 were submitted to the Agency in support of NDA 208558. Three clinical sites, Dr. Philipp Harter (Site 2601), Dr. Patricia Pautier (Site 2307), and Dr. Richard Penson (Sites 7803 and 7804), were selected for audit. The study sponsor, AstraZeneca Pharmaceuticals LP, inspection is scheduled to begin in late August 2017. At this time, there is no information from the sponsor inspection on the sponsor's conduct and oversight of Study D0816C00002.

The primary efficacy endpoint, Progression Free Survival (PFS), defined as the time from randomization until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomized therapy or received another anticancer therapy prior to progression. There were no significant inspectional findings for clinical investigators Dr. Philipp Harter, Dr. Patricia Pautier, and Dr. Richard Penson.

The data from Study D0816C00002 submitted to the Agency in support of NDA 208558, appear reliable based on available information.

II. BACKGROUND

AstraZeneca Pharmaceuticals LP, seeks approval to market olaparib for maintenance treatment in platinum-sensitive relapsed (b) (4) ovarian cancer patients who were in complete or partial response (PR) following platinum based chemotherapy. A key study supporting this application is the Phase III study, D0816C00002.

The following overview of the Study D0816C00002 is intended as background context for interpreting the inspectional findings.

Study D0816C00002 is entitled, "A Phase III Randomized, Double-Blind, Placebo Controlled, Multicenter Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy." The study was conducted at 119 clinical centers in 16 countries. A total of 295 subjects were enrolled and randomized into Study D0816C00002; 196 subjects to olaparib and 99 subjects to matching placebo.

Study Period: First subject enrolled: August 6, 2013
Data cutoff date for analysis: September 19, 2016
Primary efficacy endpoint: PFS defined as the time from randomization until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression).
Objectives of Inspections:

a. Assess PFS as determined by the clinical investigator using modified RECIST Version 1.1.
b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
c. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #1: Harter, Philipp (Site 2601) Henricistr. 92 Essen, NA 45136 Germany, Western Europe	Protocol: D0816C00002 Subjects: 10	June 19-22, 2017	Preliminary Classification NAI
CI #2: Pautier, Patricia (Site 2307) 114 rue Edouard Vaillant Villejuif Cedex, NA 94805 France, Western Europe	Protocol: D0816C00002 Subjects: 11	June 12-16, 2017	Preliminary Classification NAI

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#3: Penson, Richard **(Site 7804)** 450 Brookline Ave Boston, MA 2215 **(Site 7803)** 55 Fruit Street, Yawkey 9E, Gillette Center for Gynecologic Oncology Boston, MA 2114	Protocol: D0816C00002 Subjects: 10	April 18, 2017 – May 1, 2017	NAI
Sponsor: Astra Zeneca Study Management and Operations *Postepu 14, 02-676* *Warsaw, Poland* ***POC: Andrzei S Uzar*** *Email:* *Andrzej.Uzar@astrazeneca.com.* *Mobile:* (b) (6)	*Protocol:* *D0816C00002* *Site Numbers: 2601, 2307, 7804, 7803, and two additional randomly selected sites.*	*Delayed Start:* (b) (5)	*Preliminary Classification* *N/A*

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Philipp Harter, M.D. (Site 2601)

The site screened 14 subjects and enrolled 10 subjects. Records of all 10 enrolled subjects were reviewed during the inspection. At the time of this inspection seven subjects had completed the study, two subjects were still on study, and one subject had withdrawn consent. Four subjects were deceased. The inspection included assessment of all study related materials for Study D0816C00002: financial disclosure documentation, investigator's agreement, protocol and amendments, monitoring activities, sponsor/monitor/IEC correspondences, test article accountability, and subject records. A complete review of all informed consent documentation, AEs, SAEs, concomitant medications, randomization procedures, and eligibility criteria was performed. The source data was compared to the e-CRF and data listings submitted to the application.

The inspection revealed no significant deficiencies. Source documents at the site verified primary efficacy endpoint data as determined by the clinical investigator. There was no evidence of under-reporting of AEs.

2. Dr. Patricia Pautier, M.D. (Site 2307)

The site screened 11 subjects and enrolled 11 subjects. Records of all 11 subjects were reviewed during the inspection. At the time of this inspection ten subjects had completed the study and one subject was still on study. Six subjects were deceased. The inspection included assessment of all study related materials for Study D0816C00002; financial disclosure documentation, investigator's agreement, protocol and amendments, monitoring activities, sponsor/monitor/IEC correspondences, test article accountability, and subject records. A complete review of all informed consent documentation, AEs, SAEs, concomitant medications, randomization procedures, and eligibility criteria was performed. The source data was compared to the e-CRF and data listings submitted to the application.

The inspection revealed no significant deficiencies. Source documents at the site verified primary efficacy endpoint data as determined by the clinical investigator. There was no evidence of under-reporting of AEs.

3. Dr. Richard Penson, M.D. (Sites 7803 and 7804)

The sites screened 14 subjects and enrolled 10 subjects. Records of all enrolled subjects were reviewed during the inspection. The inspection included assessment of all informed consent forms, protocol compliance, subject source data, AE detection and reporting, IRB correspondence and approvals, and financial disclosure forms and investigator agreements. The source data was compared to the data listings submitted to the application.

The inspection revealed no significant deficiencies. Source documents at the site verified primary efficacy endpoint data as determined by the clinical investigator. With one exception, there was no evidence of under-reporting of AEs. Subject 7804-508, the last subject enrolled by Site 7804 had an adverse event (AE) that was not reported to the Sponsor. The AE was reported to the sponsor during the current inspection.

In addition, there were several noteworthy protocol deviations. Briefly, Subject 7803-503 was screened on July 7, 2014, randomized on July 10, 2014, and received their first dose of study drug on July 11, 2014. On July 25, 2014 it was discovered that this subject was determined to have stable disease (SD) based upon a screening CT scan making the subject ineligible; the subject did not meet inclusion criteria 5b, "*For the last chemotherapy course immediately prior to randomization on the study, patients must be, in the opinion of the investigator, in response (partial or complete radiological response)…*" The protocol deviation was reported to the sponsor the same day it was discovered and to the IRB six days later. Subject 7803-503, per the Sponsor, was allowed to continue on the study blinded. This subject continued on the study and all protocol requirements were met up until the subject was off study for findings of progressive disease (PD).

Subjects 7804-501 and 7804-504 were enrolled in 2014, but both subjects didn't meet Inclusion Criterion 7, which requires hemoglobin to be greater than or equal to 10g/dL within 28 days of randomization, with "no blood transfusions in the past 28 days". This was found during a monitoring visit in September 2014, and reported to the Sponsor. It was also reported to the IRB. The IRB reviewed this on October 24 2014 using their expedited review procedures. No further action was indicated since retraining of study staff had already occurred.

With the exception of the one unreported AE noted above for Subject 7804-503, the data listings submitted to the application were consistent with source documents found at these sites. Overall study files were complete and well organized.

4. Sponsor: Astra Zeneca Study Management and Operations
(Location of the Trial Master File)

The inspection of the sponsor, Astra Zeneca, of Study D0816C00002 is scheduled to begin near the end of August 2017. As soon as the inspection is completed, an assessment of preliminary findings will be conducted. The Clinical Inspection Summary will be amended to reflect the final inspectional findings upon receipt and review of the Establishment Inspection Report.

A recommendation regarding data reliability of the data submitted by Astra Zeneca to the Agency associated with Study D0816C00002 will be provided in an addendum to the CIS.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D., Team Leader and
Acting Branch Chief for
Kassa Ayalew, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm. NDA #208558
DOP1/Division Director/Geoffrey Kim
DOP1/Clinical Team Leader/Sanjeeve Bala
DOP1/Project Manager/Rajesh Venugopal
DOP1/Medical Officer/Gwynn Ison
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
07/19/2017

SUSAN D THOMPSON
07/19/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 11, 2017
To:	Julia Beaver, MD Acting Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kevin Wright, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	LYNPARZA (olaparib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208558
Applicant:	AstraZeneca Pharmaceuticals, LP

1 INTRODUCTION

On February 22, 2017, AstraZeneca Pharmaceuticals, LP submitted the last portion of a rolling submission for the Agency's review of an original New Drug Application (NDA) 208558 for LYNPARZA (olaparib) tablets. The proposed indication for LYNPARZA (olaparib) tablets is as monotherapy:

- for the maintenance treatment of patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (complete response or partial response) to platinum-based chemotherapy.
- 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on February 1, 2017, and February 23, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for LYNPARZA (olaparib) tablets.

2 MATERIAL REVIEWED

- Draft LYNPARZA (olaparib) tablets MG received on February 22, 2017, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on June 27, 2017.
- Draft LYNPARZA (olaparib) tablets Prescribing Information (PI) received on February 22, 2017 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 27, 2017.
- Approved LYNPARZA (olaparib) capsules comparator labeling dated January 26, 2017.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
07/11/2017

KEVIN WRIGHT
07/11/2017

SHAWNA L HUTCHINS
07/11/2017

LASHAWN M GRIFFITHS
07/11/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **July 11, 2017**

To: **Rajesh Venugopal, MPH, MBA**
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products

From: Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Lynparza®** (olaparib) tablets, for oral use
NDA 208558

Office of Prescription Drug Promotion comments on proposed prescribing information (PI) and container labels

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Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) and container labels for **Lynparza®** (olaparib) tablets, for oral use as requested by DOP1 in the consult dated February 23, 2017.

OPDP's review of the proposed PI is based on the draft PI titled, "sent to Sponsor_6.27.17_Submitted 2.22.17_annotated-draft-label.doc" sent by electronic mail on June 27, 2017, to OPDP (Kevin Wright) from DOP1 (Rajesh Venugopal). OPDP's comments are listed in the attached PI.

OPDP also reviewed the proposed container labels and carton labeling submitted to the electronic document on July 6, 2017. OPDP has no comments for the proposed container labels.

The combined OPDP and Division of Medical Policy Programs (DMPP) review of the patient package insert (PPI) will be provided under a separate cover.

If you have any questions, please feel free to contact, Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

KEVIN WRIGHT
07/11/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	July 10, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 208558
Product Name and Strength:	Lynparza (olaparib) tablets, 100 mg and 150 mg
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
Submission Date:	July 6, 2017
OSE RCM #:	2017-225-1
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Oncology Products 1 requested that we review the revised Lynparza container labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised Lynparza container labels are acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Gao T. Label and Labeling Review for Lynparza (NDA 208558). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 June 21. RCM No.: 2017-225.

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/s/

TINGTING N GAO
07/10/2017

CHI-MING TU
07/10/2017

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 21, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 208558
Product Name and Strength:	Lynparza (olaparib) tablets, 100 mg and 150 mg
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
Submission Date:	June 14, 2017 and June 15, 2017
OSE RCM #:	2017-225
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Lynparza (olaparib) is currently marketed as capsules. AstraZeneca submitted an original 505(b)(1) NDA proposing to market Lynparza (olaparib) as a tablet formulation that that will ultimately replace the currently marketed Lynparza capsule formulation.[a] AstraZeneca also explained that Lynparza tablets (100 mg and 150 mg) are not interchangeable with Lynparza capsules (50 mg) due to differences in the dosing of each formulation.

This review evaluates the submitted Lynparza container labels and Prescribing Information (PI) to identify areas of vulnerability that could lead to medication errors in response to a consult request from Division of Oncology Products 1 (DOP1).

1.1 REGULATORY HISTORY

AstraZeneca proposed an initial risk mitigation strategy[b] and a supplemental risk mitigation strategy[c] to address the potential risks associated with introduction of olaparib tablets to the US market following approval of NDA 208558. Specifically, AstraZeneca stated in this analysis that all new Lynparza prescriptions will be for the tablet formulation and the capsules will ultimately be removed from the US market, approximately (b) (4) after launch of the tablets. AstraZeneca also proposed (b) (4) However, due to risk of inadvertent substitution of Lynparza tablets and capsules, the Division of Oncology Products 1 (DOP1) and DMEPA held a teleconference with AstraZeneca on May 18, 2017.[d] Post-teleconference, AstraZeneca agreed to restrict distribution of the Lynparza capsule formulation to only Specialty Pharmacies prior to the introduction of the Lynparza tablet formulation to the US market. This will help to ensure that the two formulations do not coexist outside the AstraZeneca SP network.[e] DMEPA believes that these additional mitigation strategies provides further assurance in terms of preventing medication errors between the tablets and capsules, and thus find AstraZeneca's proposal acceptable.

2 MATERIALS REVIEWED

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[a] AstsraZeneca. Type B Pre-NDA Meeting Briefing Document Appendix B: LYNPARZA Education Plan Details. Gaithersburg (MD): AstsraZeneca Pharmaceuticals LP. 2016 December 14. IND 075918.

[b] AstsraZeneca. Failure Mode and Effects Analysis for the Risk of Medication Errors with the Introduction of a Tablet Formulation for Olaparib. Gaithersburg (MD): AstsraZeneca Pharmaceuticals LP. 2017 February 22. NDA 208558.

[c] AstsraZeneca. Lynparza™ (olaparib) tablets - NDA 208,558. Lynparza Proprietary Name Request Amendment and Risk Mitigation Strategy. Gaithersburg (MD): AstsraZeneca Pharmaceuticals LP. 2017 May 16. NDA 208558.

[d] Venugopal, R. Memorandum of Teleconference (NDA 208558). Silver Spring (MD): FDA, CDER, OND, DOP1 (US); 2017 May 23. NDA 208558.

[e] AstsraZeneca. Lynparza™ (olaparib) tablets - NDA 208,558. Lynparza Risk Mitigation Strategy: Modification of Capsule Dispensing Network. Gaithersburg (MD): AstsraZeneca Pharmaceuticals LP. 2017 June 6. NDA 208558.

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed oral tablet formulation for Lynparza (100 mg and 150 mg) is not bioequivalent thus not substitutable with the currently marketed Lynparza oral capsule formulation. (b) (4) , Lynparza tablet has an improved bioavailability compared with the capsule formulation.[f] To minimize the risk of medication errors, AstraZeneca proposed to update the text on the container labels to "Attention: Lynparza tablets and capsules are NOT (b) (4). Do NOT take more than 4 Tablets a day."

3.1 PRESCRIBING INFORMATION (PI)

We evaluated the Lynparza PI and recommend moving the information regarding non-substitutability between Lynparza capsules and Lynparza tablets to Section 2.1 since Lynparza tablets have higher bioavailability than Lynparza capsules and may lead to overdose or underdose errors if the two formulations are confused. Furthermore, we recommend to use the term "DO NOT substitute" instead of "(b) (4)" since the term (b) (4)" is reserved for biosimilar products.

3.2 CONTAINER LABEL

We evaluated the Lynparza container labels and identified the following concerns from a medication error perspective:

[f] AstsraZeneca. Type B Pre-NDA Meeting Briefing Document for Drug substance Olaparib (AZD2281, KU-0059436). Gaithersburg (MD): AstsraZeneca Pharmaceuticals LP. 2016 December 14. IND 075918.

- The NDC numbers are presented as a placeholder “XXXX-XXX-XX”. We are unable to determine whether the NDC product code numbers will adequately differentiate the 100 mg and 150 mg strength products.
- The net quantity statement (“60 Tablets” and “120 Tablets”) immediately below the strength statement may result in numerical confusion between the strength and net quantity.
- The statement “Attention: Lynparza Tablets and Capsules are NOT [redacted]. Do NOT take more than 4 Tablets a day.” utilizes the term “[redacted]” that refers to biosimilar products.
- The “[redacted]” statement makes the information on the principal display panel appear crowded and visually cluttered.
- The storage statements do not contain the temperature scale designation (i.e., “°C” or “°F”) after each numerical value. We are concerned that the acceptable storage temperature could be misinterpreted and pose risk of improper storage leading to decrease product quality.

4 CONCLUSION & RECOMMENDATIONS

The proposed Lynparza PI and container labels require revision to ensure safe product use. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section
   Revise the phrase “[redacted]” to “DO NOT substitute” because the term “[redacted]” refers to biosimilar products, thus making the proposed Lynparza Tablet that is not a biosimilar product misleading. Additionally, relocate the statement to above Section 2.1 to increase the prominence of this important information to ensure safe use:

   > Lynparza is also available as a 50 mg capsule. DO NOT substitute Lynparza tablets (100 mg and 150 mg) with Lynparza capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation [see Clinical Pharmacology (12.3)]. Refer to the full prescribing information for Lynparza capsules for specific capsule dosing.

4.2 RECOMMENDATIONS FOR ASTRAZENECA

We recommend the following be implemented prior to approval of this NDA:

A. Container labels

1. The NDC numbers are presented as a placeholder "XXXX-XXXX-XX". Ensure that the product codes (the middle 3 digits -XXX-) in the NDC numbers are non-sequential between the product strengths. Assignment of sequential numbers for product codes is not an effective differentiating feature (e.g. -666-, -667-, and -668-), which may lead to selecting and dispensing of wrong drug.
2. Relocate the net quantity statement ("60 Tablets" and "120 Tablets") away from the strength so that it does not compete for prominence with the strength statement and minimize the risk of numerical confusion between the strength and net quantity. This can be achieved by relocating the net quantity statement to immediately below the "Attention: Lynparza Tablets and Capsules…" statement.
3. Revise the statement "Attention: Lynparza Tablets and Capsules are NOT (b) (4) Do NOT take more than 4 Tablets a day." to read "Attention: Lynparza Tablets and Capsules are NOT substitutable. Do NOT take more than 4 Tablets a day." because the term " (b) (4)" refers to biosimilar products, thus making the proposed Lynparza Tablet that is not a biosimilar product misleading. Additionally, add a rectangular outline around the text to increase its prominence.
4. Remove the " (b) (4)" statement since it is not required per 21 CFR 201.100(b)(3) for oral products and to reduce information crowding on the principal display panel.
5. The storage statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that the acceptable storage temperature could be misinterpreted and pose risk of improper storage leading to decrease product quality. Ensure that the degree symbol and temperature scale follows each numeric value denoting temperature ranges. For example, revise "15-30°C" to read "15°C - 30°C".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lynparza tablets that AstraZeneca submitted on June 14, 2017, and Lynparza capsules retrieved from March 17, 2016 approved Lynparza capsules Prescribing Information.[g]

Table 2. Relevant Product Information for the currently marketed Lynparza capsules and proposed Lynparza tablets

Product Name	**Lynparza capsule (NDA 206162)**	**Lynparza tablet (NDA 208558)**
Initial Approval Date	December 19, 2014	N/A
Active Ingredient	Olaparib	Olaparib
Indication	Indicated 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. The indication is approved under accelerated approval based on objective response rate and duration of response.	Indicated as monotherapy: • for the maintenance treatment of patients with platinum-sensitive **relapsed epithelial ovarian, fallopian tube or primary peritoneal cancer**, who are in response (complete response or partial response) to platinum-based chemotherapy. • 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.
Route of Administration	Oral	Oral
Dosage Form	**Capsule**	**Tablet**
Strength	**50 mg**	**100 mg, 150 mg**

[g] Lynparza. Drugs@FDA. U.S. Food and Drug Administration; January 2017. [cited 2017 March 23]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/206162s003lbl.pdf.

Table 2. Relevant Product Information for the currently marketed Lynparza capsules and proposed Lynparza tablets		
Product Name	**Lynparza capsule (NDA 206162)**	**Lynparza tablet (NDA 208558)**
Dose and Frequency	The recommended dose is 400 mg (eight 50 mg capsules) taken orally twice daily with or without food, for a total daily dose of 800 mg. Dose reduction for ADR: • 200 mg (four 50 mg capsules) taken twice daily, for a total daily dose of 400 mg. • May further reduce to 100 mg (two 50 mg capsules) taken twice daily, for a total daily dose of 200 mg. Dose reduction for use with CYP3A inhibitors: • 150 mg (three 50 mg capsules) taken twice daily for a strong CYP3A inhibitor • 200 mg (four 50 mg capsules) taken twice daily for a moderate CYP3A inhibitor Dose reduction for patient with moderate renal impairment (CLcr 31-50 mL/min): • 300 mg (six 50 mg capsules) taken twice daily, for a total daily dose of 600 mg	Recommended dose is 300 mg (two 150 mg tablets) taken orally twice daily with or without food, for a total daily dose of 600 mg. Dose reduction for ADR: • 250 mg (one 150 mg tablet and one 100 mg tablet) taken twice daily, for a total daily dose of 500 mg. • May further reduce to 200 mg (two 100 mg tablets) taken twice daily, for a total daily dose of 400 mg. Dose reduction for use with CYP3A inhibitors: • 100 mg (one 100 mg tablet) taken twice daily (equivalent to a total daily dose of 200 mg) for a strong CYP3A inhibitor • 150 mg (one 150 mg tablet) taken twice daily (equivalent to a total daily dose of 300 mg) for a moderate CYP3A inhibitor Dose reduction for patient with moderate renal impairment (CLcr 31-50 mL/min): • 200 mg (two 100 mg tablets) twice daily, for a total daily dose of 400 mg
How Supplied	Bottles of 112 capsules	Bottle of 60 tablets and 120 tablets

Table 2. Relevant Product Information for the currently marketed Lynparza capsules and proposed Lynparza tablets		
Product Name	**Lynparza capsule (NDA 206162)**	**Lynparza tablet (NDA 208558)**
Storage	Store at 25ºC (77°F), excursions permitted to 15ºC -30ºC (59ºF - 86ºF) [see USP Controlled Room Temperature] Lynparza should not be exposed to temperatures greater than 40ºC or 104ºF. Do not take Lynparza if it is suspected of having been exposed to temperatures greater than 40ºC or 104ºF.	Store at 25ºC (77°F), excursions permitted to 15ºC -30ºC (59ºF - 86ºF) [see USP Controlled Room Temperature]. Store in original bottle to protect from moisture.
Container Closure	The bottle pack is a 190 mL bottle made of white, high-density polyethylene (HDPE) with a (b) (4) cap made of (b) (4) Inside the cap there is a liner and seal. The liner is made of wax-coated pulp board and the seal is aluminium foil lined with (b) (4).	The primary pack is a 110 and a 190 mL bottle made of white, high-density polyethylene (HDPE) with a (b) (4) screw closure made of (b) (4) Inside the bottle are desiccant containers, containing silica gel.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 23, 2017, we searched the L:drive and AIMS using the terms, Lynparza to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 1 previous review[h] for Lynparza capsules, which is not relevant for this review since this review is for Lynparza tablets.

[h] Mathew, D. Label and Labeling Review for Lynparza (Olaparib) Capsules (NDA 206162). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 21. RCM No.: 2014-343.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On March 23, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, and Nursing
Search Strategy and Terms	Match Any of the Words: Lynparza olaparib

D.2 Results

The search did not retrieve any articles.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

TINGTING N GAO
06/21/2017

CHI-MING TU
06/21/2017

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 8, 2017

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Rajesh Venugopal, RPM
DOP1

Subject: QT-IRT Consult to NDA 208558

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 03/06/2017 regarding the sponsor's proposed labeling language related to QT. The QT-IRT received and reviewed the following materials:

- Your consult;
- Sponsor's proposed labeling; and
- Previous QT-IRT review under NDA 206162 (dated 11/18/2014 in DARRTS)

The Division has requested the review of following language related to QT effects proposed by the sponsor in the label:

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of olaparib on cardiac repolarization was assessed in 119 patients following a single dose of 300 mg and in 109 patients following multiple dosing of 300 mg twice daily. No clinically relevant effect of olaparib on QT interval was observed.

QT-IRT Comments for DOP1

QT-IRT's following proposed labeling language is a suggestion only and it is based on already provided labeling language in the previous QT-IRT review (under NDA 206162; dated 11/18/2014 in DARRTS) that analyzed the data from the pooled studies. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of olaparib on the QTc interval was evaluated in a pooled study in 119 patients with solid tumors. No large changes in the mean QTc interval (>20 ms) were detected in the study at the therapeutic drug exposure.

Thank you for requesting our input into the development of this product under NDA 208558. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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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.

/s/

DHANANJAY D MARATHE
05/08/2017

CHRISTINE E GARNETT
05/08/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208558	NDA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)

Proprietary Name: Lynparza™
Established/Proper Name: olaparib
Dosage Form: Tablets
Strengths: 100 mg, 150 mg
Route(s) of Administration: Oral

Applicant: AstraZeneca Pharmaceuticals LP
Agent for Applicant (if applicable): N/A

Date of Application: February 22, 2017
Date of Receipt: February 22, 2017
Date clock started after Unacceptable for Filing (UN): N/A

PDUFA Goal Date: August 22, 2017	Action Goal Date (if different):
Filing Date: April 23, 2017	Date of Filing Meeting: March 20, 2017

Chemical Classification (original NDAs only) :

☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☒ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch
☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval)
☒ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)

Proposed indication(s)/Proposed change(s): Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy:

☐ for the maintenance treatment of patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (complete response or partial response) to platinum-based chemotherapy.

☐ 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.

Type of Original NDA: AND (if applicable) Type of NDA Supplement: N/A ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☒ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☒ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☒ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 75918	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive?	☐	☒		Drug name is incorrect in DARRTS. It currently reads "Lynpraza" instead

If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.				of "Lynparza".
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** *http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm* ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** *http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf*	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		

• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable	☐	☐		

standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837 htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒		☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☐	☐ ☐	☐ ☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	CDRH – 2/1/17 OSI Clinical Inspection – 3/21/17 IRT/QT – 3/6/17
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** November 18, 2009	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** January 12, 2017	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 20, 2017

BACKGROUND: AstraZeneca has submitted an NDA for a new tablet formulation of olaparib [NDA 208558 (olaparib) Tablets, 100 mg, 150 mg] for the maintenance treatment of second line platinum-sensitive relapsed (PSR) ovarian cancer regardless of BRCA mutation status based on two pivotal studies, SOLO2 and Study 19.

This application is intended to provide confirmatory evidence that olaparib has an acceptable benefit:risk profile in ovarian cancer and also requests that the indication awarded to the capsules in NDA 206162 be granted to the tablet formulation of olaparib.

The NDA was submitted to the Agency via rolling submission in which the final piece of the submission was submitted on February 22, 2017. This is a non-NME priority review with a 6 month goal date of August 22, 2017.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Rajesh Venugopal	Y
	CPMS/TL:	Christy Cottrell	Y
Cross-Discipline Team Leader (CDTL)	Sanjeeve Balasubramaniam		Y
Division Director/Deputy	Geoffrey Kim		Y
Office Director/Deputy	Richard Pazdur		Y
	Reviewer:	Gwynn Ison	Y
	TL:	Sanjeeve Balasubramaniam	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Runyan Jin	Y
	TL:	Qi Liu	N
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	Chao Liu	Y
Biostatistics	Reviewer:	Stella Karuri	Y
	TL:	Shenghui Tang	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tiffany Ricks	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Xiao-Hong Chen	Y
	RBPM:	Kristine Leahy	N
• Drug Substance	Reviewer:	Gaetan Ladouceur	Y
• Drug Product	Reviewer:	Olen Stephens	Y
• Process	Reviewer:	Hong Wen	Y
• Microbiology	Reviewer:	N/A	
• Facility	Reviewer:	Steve Hertz	Y
• Biopharmaceutics	Reviewer:	Jing Li	Y
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	CDRH: Soma Ghosh, Eunice Lee, Reena Philips		Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Sharon Mills	Y
	TL:	Barbra Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Kevin Wright	Y
	TL:	Trung-Hieu Tran	Y
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Tingting Gao	Y
	TL:	Alice Tu	Y
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connors	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	Katherine Fedenko (Safety)		Y
	Christina Marshall (Safety)		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julia Beaver, MD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
03/24/2017

CHRISTY L COTTRELL
03/24/2017