CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME 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)

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Date of This Review:	May 18, 2017
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
Panorama #:	2017-13394472
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD
DMEPA Acting Deputy Director:	Danielle Harris, PharmD, BCPS
DMEPA Director:	Todd Bridges, RPh

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Lynparza, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

Lynparza (olaparib) Capsules were approved on December 19, 2014 under NDA 206162. The Applicant submitted the name, Lynparza, for the new dosage form tablets for review under NDA 208558 on February 27, 2017.

The proposed Lynparza tablets are not bioequivalent with the currently marketed Lynparza capsules.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 27, 2017 proprietary name submission.

Table 1. Relevant Product Information for Lynparza

Product Name	**Lynparza (NDA 206162)**	**Proposed proprietary name Lynparza (NDA 208558)**
Initial Approval Date	December 19, 2014	Currently under review
Intended Pronunciation	Lin-par-zah	Lin-par-zah
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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.	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

Table 1. Relevant Product Information for Lynparza		
Product Name	**Lynparza (NDA 206162)**	**Proposed proprietary name Lynparza (NDA 208558)**
Dosage Form	Capsules[1]	Tablets[1]
Strength	50 mg	100 mg, 150 mg
Dose and Frequency	The recommended dose of Lynparza 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 To manage adverse reactions, consider interruption of treatment or dose reduction. • 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

[1] Lynparza tablets are not bioequivalent with Lynparza capsules.

Table 1. Relevant Product Information for Lynparza		
Product Name	**Lynparza (NDA 206162)**	**Proposed proprietary name Lynparza (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 aluminum 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.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Oncology Products 1 (DOP1) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[2].

[2] USAN stem search conducted on March 6, 2017.

2.2.2 Components of the Proposed Proprietary Name

The Applicant did not provide a derivation or intended meaning for the proposed name, Lynparza, in their submission. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, March 14, 2017 e-mail, the Division of Oncology Products 1 (DOP1) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.4 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving Lynparza capsules that would be relevant for this review.

Table 2. FAERS Search Strategy	
Search Date	March 2, 2017
Drug Name	Lynparza [product name]
Event (MedDRA Terms)	**DMEPA Official PNR Name Confusion Search Terms Event List:** Preferred Terms: CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR DRUG ADMINISTRATION ERROR) DRUG DISPENSING ERROR DRUG PRESCRIBING ERROR INTERCEPTED DRUG DISPENSING ERROR INTERCEPTED DRUG PRESCRIBING ERROR INTERCEPTED MEDICATION ERROR MEDICATION ERROR PRODUCT NAME CONFUSION TRANSCRIPTION MEDICATION ERROR Lower Level Terms: INTERCEPTED PRODUCT SELECTION ERROR INTERCEPTED WRONG DRUG PRODUCT SELECTED INTERCEPTED WRONG DRUG SELECTED PRODUCT SELECTION ERROR WRONG DEVICE DISPENSED WRONG DRUG ADMINISTERED WRONG DRUG DISPENSED WRONG DRUG PRESCRIBED

	WRONG DRUG PRODUCT SELECTED WRONG DRUG SELECTED WRONG PRODUCT SELECTED
Date Limits	Up to March 1, 2017

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, 2 reports were not included in the final analysis for the following reasons: adverse event not related to medication error (n=1) and off label use (n=1).

Following exclusions, we did not identify any case of name confusion medication errors relevant to this review.

2.2.5 Safety Analysis of Multiple Dose Forms Under the Same Proprietary Name

The usual dose of the currently marketed Lynparza capsules is 400 mg (eight 50 mg capsules) twice daily. The proposed olaparib tablets are not bioequivalent to the currently marketed capsules, and the usual dose for the tablet formulation is 300 mg (two 150 mg tablets) twice daily. The proposed olaparib tablets are 1.5 to 1.8 folds more bioavailable than the capsule formulation per the DOP1 Review Team. Because the doses (either 400 mg or 300 mg) are achievable with either dosage form, we are concerned about wrong dosage from medication errors during dispensing, especially when prescribers may not indicate the dosage form on a prescription. Also, in clinical practice, healthcare practitioners (HCP) often do not expect a difference between tablets and capsules, and often substitute the tablets and capsules when it is for the same drug. In this case, if the proposed olaparib tablets are marketed under Lynparza, then HCP may inadvertently substitute Lynparza capsules and tablets. For example, if a prescription for Lynparza 400 mg that is intended for capsules is mistakenly dispensed as four 100 mg tablets, then an overdose will occur because the tablets are more bioavailable.

AstraZeneca (AZ) submitted a "Failure Mode and Effects Analysis for the Risk of Medication Errors with the Introduction of a Tablet Formulation for Olaparib" as a part of the original NDA submission on February 22, 2017. AZ 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. We sent an Information Request to AZ on April 18, 2017 for more information, to which AZ responded that promotional activities, HCP instructions, and limiting distribution of Lynparza capsules would encourage HCP to prescribe Lynparza tablets. AZ stated because Lynparza tablets reduce pill burden, they plan to recommend HCP start new patients on the tablets. Additionally, AZ re-stated they plan to continue to market Lynparza capsule for another (b) (4) after Lynparza tablet approval but the capsules will be phased out in the US. AZ's response did not alleviate our concern for the risk of wrong dosage from medication errors.

We communicated our concerns to the DOP1 Review Team, and they agreed with our concerns. We held a teleconference with AZ on May 9, 2017 to inform AZ of our concerns for wrong

dosage form medication errors during dispensing and the resultant overdose. At the teleconference, AZ stated the risk of such error could be mitigated with limiting distribution to specialty pharmacies, education, and prior authorization. As this was new information, DMEPA requested AZ to submit their strategies to prevent such medication errors in writing as an amendment to the proprietary name submission. AZ submitted the amendment on May 16, 2017.

In the May 16, 2017 amendment (See Appendix A), AZ asserted the combination of controlled distribution/pharmacy systems, education, payer controls, and messaging to clarity dosing and drive tablet use such will effectively mitigate risk.[3] AZ also noted there are (b) (4) patients in the US who are currently taking Lynparza capsules. We considered the following AZ submitted in the amendment in our evaluation of the proposed proprietary name, Lynparza, for the tablet formulation:

1. Controlled distribution/pharmacy systems
   Lynparza capsules are currently dispensed by 2 specialty pharmacies (i.e., (b) (4)) that account for (b) (4)% of patients on Lynparza, and hospital/physician practices that account for (b) (4)% of patients on Lynparza. Within (b) (4) (b) (4) of Lynparza tablet approval, Lynparza capsules will be consolidated to the 2 existing specialty pharmacies for 100% of patients who remain on the capsule formulation. Furthermore, the median duration of Lynparza capsule therapy is (b) (4) months based on market data.

   Lynparza tablets will be available through the 2 specialty pharmacies and hospital/physician practices, with an anticipated approximately (b) (4)% of Lynparza tablets dispensing via specialty pharmacies.

   Specialty pharmacies coordinate many aspects of patient care, so AZ expects the high level of patient support will prevent the risk of wrong dosage form medication errors during dispensing (See Appendix A, Table 1).

2. Education
   Both specialty pharmacies (i.e., (b) (4) .) and all hospital/physician practices will be trained by AZ medical affairs and/or commercial personnel. AZ will educate pharmacy staff on the new tablet formulation and dosing differences between the tablet and capsule formulations. Specialty pharmacies and hospital/physician practices will be contacted both prior to and following tablet approval.

   Patient-friendly education materials on appropriate tablet dosing will also be distributed along with an optional enrollment into "My Lynparza" patient support program.

3. Payer controls
   Payment authorization (prior authorization) is required prior to dispensing Lynparza. If a pharmacy tries to dispense an excess quantity of Lynparza tablets at the 400 mg twice daily dosing, then the prior authorization will deny payment.

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[3] AstsraZeneca. Lynparza Proprietary Name Request Amendment and Risk Mitigation Strategy. Gaithersburg (MD): AstsraZeneca Pharmaceuticals LP. 2017 May 16. NDA 208558.

After evaluation of AZ's mitigation strategies, we agree that the combination of aforementioned efforts will help to mitigate the risk of wrong dosage form medication errors. Although AZ may not be able to control the types of stops insurance companies will put in place for Lynparza prior authorizations, it is reasonable to expect Lynparza to have a prior authorization. We normally do not think limiting distribution to specialty pharmacy will prevent wrong drug errors between specialty drugs and non-specialty drugs based on our post-marketing experience. However, we recognize in this Lynparza case it is the same active ingredient product where the capsules will only be dispensed through specialty pharmacies after (b) (4) from Lynparza tablet approval. In the specialty pharmacies (b) (4)., we agree with AZ that the close monitoring and frequent contacts with the patients made by specialty pharmacists will likely help to mitigate the risk of wrong dosage form errors. The eventual discontinuation of Lynparza capsules in the US will also eliminate the risk of wrong dosage form errors all together.

The risk remains in the (b) (4) period where both dosage forms may also be dispensed from a hospital/physician practice for those anticipated (b) (4)% of patients (b) (4) patients currently on Lynparza capsules). The education proposed is the critical component to prevent wrong dosage form errors during this period. AZ plans to educate both specialty pharmacies and all hospital/physician practices that dispense Lynparza both prior to and following tablet approval. Also, the (b) (4) median duration of therapy suggests patients currently on Lynparza capsules will discontinue the capsules within that (b) (4) period. For the few patients who choose to continue the capsule formulation, they would be managed by a specialty pharmacy for their Lynparza dispensing after the (b) (4) period.

Given the totality of information considered and the mitigation strategies proposed by the Applicant (see Appendix A), we determined in this specific scenario, it is acceptable for the proposed tablet formulation to be marketed under the same proprietary name, Lynparza.

2.2.6 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Oncology Products 1 (DOP1) during the Midcycle Meeting on May 16, 2017.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Lynparza, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your February 27, 2017 submission and May 16, 2017 amendment are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Description of FAERS***

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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/s/

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05/18/2017

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