CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208558
Review #1

Drug Name/Dosage Form	LYNPARZA® (olaparib) Tablets
Strength	100 mg and 150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AstraZeneca
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Rolling submission (0000)	12/9/2016	DS/DP/Process/Biopharm./Facility/EA
Original NDA (0002)	2/22/2017	DS/DP/Process/Biopharm./Facility/EA
Quality Amendment (0013)	4/5/2017	DP/ Biopharm.
Quality Amendment (0016)	4/21/2017	Process
Quality Amendment (0030)	6/1/2017	DP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gaetan Ladouceur	CDER/OPQ/ONDP/DNDAPI
Drug Product	Olen Stephens	CDER/OPQ/ONDP/DNDP1
Process	Hong Wen	CDER/OPQ/OPF/DPAIII
Microbiology	N/A	
Facility	Steve Hertz	CDER/OPQ/OPF/DIA
Biopharmaceutics	Jing Li	CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI
Application Technical Lead	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
Laboratory (OTR)	N/A	
ORA Lead	Caryn McNab	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Analysis (EA)	Olen Stephens	CDER/OPQ/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	Previously reviewed for ANDA	Per MaPP 5015.5 no review of DMF is necessary.
	Type III			Adequate	Previously reviewed for ANDA	Per MaPP 5015.5 no review of DMF is necessary.
	Type III			Adequate	Previously reviewed for ANDA	Per MaPP 5015.5 no review of DMF is necessary.
	Type III			Adequate	Previously reviewed for ANDA	Per MaPP 5015.5 no review of DMF is necessary.
	Type III			Adequate	Previously reviewed for ANDA	Per MaPP 5015.5 no review of DMF is necessary.
	Type III			Adequate	Previously reviewed for ANDA	Per MaPP 5015.5 no review of DMF is necessary.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75918	Initial IND was submitted on 08/23/2006

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The CMC information provided in the NDA has been reviewed and found to be complete and acceptable. There are no outstanding deficiencies with the application. The NDA is recommended for **Approval** from the product quality perspective.

The action letter should include the following language:

A shelf life of 36 months is granted (b) (4) *for both the 100 mg and 150 mg tablets when stored in the HDPE bottle configuration with desiccants under the labeled conditions of "store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature".*

(b) (4)

II. Summary of Quality Assessments

A. Product Overview

Olaparib is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed epithelial ovarian, fallopian tube or primary peritoneal cancer and treatment of patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer. Olaparib 50 mg capsules received accelerated approval (NDA 206162) for the treatment of ovarian cancer on December 19, 2014 under. The recommended dose of olaparib capsules is 400 mg bid po, and the patients are required to take 8 capsules bid with current approved formulation. To improve convenience for patients, an oral tablet formulation containing 100 mg and 150 mg of olaparib was developed, and submitted in this NDA. CMC information for the drug substance remains mostly unchanged. Olaparib has very low aqueous solubility and poor bioavailability. (b) (4) This makes the tablet formulation more bioavailable that the

(b) (4) The recommended dose for the tablet formulation is 300 mg twice daily (BID) instead of 400 mg (BID) for the capsule formulation.

The proposed shelf-life for Olaparib Tablets, 100 mg and 150 mg, is 36 months, and is deemed acceptable based on the submitted stability data.

Proposed Indication(s) including Intended Patient Population	Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor 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.
Duration of Treatment	Continue treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	Recommended tablet dose is 300 mg taken orally twice daily with or without food
Alternative Methods of Administration	N/A

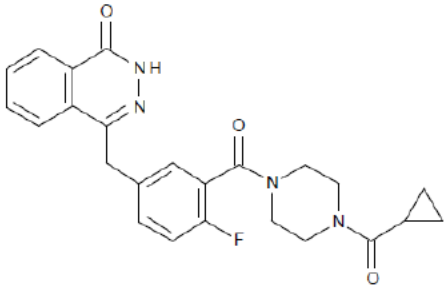
B. Quality Assessment Overview

Drug Substance

- Chemical Name and Structure:

IUPAC Name: Olaparib

Structure:



Molecular formula: $C_{24}H_{23}FN_4O_3$

Molecular Weight: 434.46

Olaparib is already available in the US as a 50 mg capsule (NDA 206162). Olaparib has no chiral center and is manufactured as a free base. It is not hygroscopic and has a very

low solubility in aqueous solutions (classified as Class 4 according to the Biopharmaceutical Classification System). The partition coefficient for the drug substance between octanol and water at 25°C is log P = 1.49. The drug substance is manufactured by (b) (4). In the currently approved NDA 206162, (b) (4) This makes the tablet formulation more bioavailable that the capsule formulation. The current drug substance manufacturing process remains the same as the previously described in NDA 206162.

The drug substance is stable in the long-term studies (36 months) and accelerated conditions (6 months). No extraordinary storage precautions are required. A retest period of (b) (4) months at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

Drug Product

The approved dose for the marketed capsule formulation of olaparib is 400 mg taken twice daily (BID), which requires 8 capsules of 50 mg strength each dose administration. The more patient-friendly tablet formulation of olaparib that delivers a therapeutic dose in fewer dose units is developed in the NDA. (b) (4) As a result, the capsule and tablet formulations are not bioequivalent. The recommended and equivalent dose for the tablet formulation is 300 mg twice daily (BID).

Following approval of the proposed NDA, two formulations of olaparib will be on the market for use in ovarian cancer patients in the US. While the two formulations are distinctly different in terms of appearance, packaging and strength, availability of both formulations in the marketplace creates the potential for medication errors. AstraZeneca is proposing a strategy for mitigating potential risk, a key component of which is to expedite removal of capsules from the US market.

Olaparib is classified as genotoxic in accordance with the ICH guidance on 'Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (ICH S2 Guideline), having tested positive in Chinese Hamster Ovary (CHO) and in vivo rat bone marrow micronucleus assay. The approach for the control of potential genotoxic impurities is consistent with ICH S9. Drug related impurities that are present at levels higher than ICH Q3A qualification threshold have been discussed and confirmed with the pharm/tox reviewer for the NDA.

(b) (4)

(b) (4) FDA will determine the filing category for this supplement at the time of its submission.

(b) (4)

Process

Manufacturing process consists of (b) (4)

Facility

Drug Substance Manufacturers:

1) (b) (4) FEI (b) (4), is acceptable
2) (b) (4) FEI (b) (4), is acceptable
3) AstraZeneca UK Ltd, FEI 3002850317, is acceptable

Drug Product Manufacturers:

1) AbbVie Deutschland, GmbH and Co. KG, FEI 3002807401, is acceptable
2) AstraZeneca, Pharmaceuticals LP, FEI 2517100, is acceptable
3) AstraZeneca UK Ltd, FEI 3002850317, is acceptable

All manufacturing facilities are deemed acceptable based on the review of cGMP history and product manufacturing profiles.

Biopharmaceutics

Olaparib is provided as an immediate release tablet. Olaparib does not exhibit pH dependent solubility and is a 'low solubility' drug under the Biopharmaceutics Classification System (BCS) at the proposed dose. The proposed dissolution method is adequate for quality control of the drug product. The proposed dissolution acceptance criteria are supported by the data provided and are acceptable. (b) (4)

The FDA-approved dissolution method as well as the acceptance criteria that were agreed to with the Applicant are as follows:

Dissolution Method	Apparatus	USP I
	Medium	50 mM pH 6.8 phosphate buffer

	Medium volume	900 mL
	Rotation speed	100 rpm
	Deaeration of medium	Yes
	Temperature in vessel	37 °C
	Analytical method	HPLC
Acceptance Criteria		100 mg: NLT (b)(4)% (Q) in 45 min 150 mg: NLT (b)(4)% in 30 min NLT (b)(4)% (Q) in 60 min

The pivotal Phase III Study D0816C00002 (SOLO2) which was designed to support the approval of the tablet formulation was conducted with the tablets of the proposed commercial formulation and manufactured at the commercial site and scale. Therefore, there is no bridging required between the clinical and commercial product. No biowaiver request was submitted in the NDA. Both the proposed strengths (100 mg and 150 mg) were used in the pivotal clinical trials to demonstrate efficacy and safety.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

Application Technical Lead Name and Date:

Xiao Hong Chen, Ph.D.
19-July-2017

Xiao Chen

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Date: 7/28/2017 12:20:01PM
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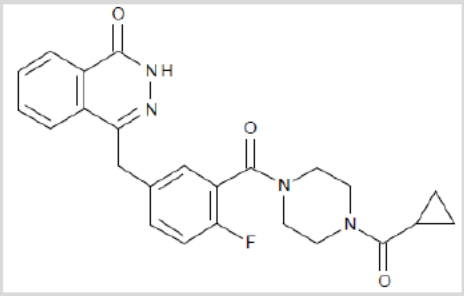
DRUG SUBSTANCE

Product Background:

NDA/ANDA:	**208558**
Chemical Name and Structure:	**Olaparib**



DMF # (if applicable):	**None**
Applicant Name/DMF Holder:	**ASTRAZENECA Pharmaceuticals**

Review Summary:

Olaparib is already available in the US as a 50 mg capsule (NDA 206162). The drug substance has no chiral center and is manufactured as a free base. It is not hygroscopic and has a very low solubility in aqueous solutions (classified as Class 4 according to the Biopharmaceutical Classification System). (b) (4)

Otherwise, the current manufacturing process remains the same than previously described in NDA 206162. Note that in this application, the limit of a related impurity (b) (4) (b) (4) % in the drug substance specification and was found acceptable.

The drug substance is stable in the long-term studies (36 months) and accelerated conditions (6 months). No extraordinary storage precautions are required. A retest period of (b) (4) months at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

List Submissions being reviewed (table):

Submission (s) Reviewed	eCTD sequence #	DARRTS SD#	Submit Date	Received Date
Original NDA	001	001	12/09/2016	12/09/2016
Quality/Response To Information	002	003	01/23/2017	01/23/2017

Highlight Key Outstanding Issues from Last Cycle:

None

Concise Description Outstanding Issues Remaining:

None

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Gaetan Ladouceur

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Ben Stevens

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Date: 7/10/2017 09:31:52AM
GUID: 5432b4d800086115752a874a47534532

DRUG PRODUCT

Product Background:

Lynparza (olaparib) capsules, 50 mg, received accelerated approval on 19-Dec-14 under NDA 206-162. Accelerated approval pathways require further adequate and well-controlled studies to verify and describe clinical benefit. This application is intended to provide confirmatory evidence that olaparib has an acceptable benefit-risk profile in ovarian cancer and convert the olaparib capsule accelerated approval to full approval. NDA 208-558 seeks full approval of the tablet formulation of olaparib tablets for the maintenance treatment of second line platinum-sensitive relapsed (PSR) ovarian cancer and is based on two pivotal studies, SOLO2 and Study 19. SOLO2 was a Phase 3 randomized, double-blind, placebo-controlled, multicenter study that investigated olaparib as a maintenance treatment in *gBRCAm* PSR ovarian cancer patients. Patients with platinum-sensitive (based upon the penultimate platinum regimen) relapsed disease who were in response (CR or PR) to their final platinum regimen and who had received at least two previous lines of platinum-based therapy were randomized to receive either olaparib or placebo. The primary endpoint was investigator-assessed progression free survival (PFS). SOLO2 was conducted with a tablet formulation of olaparib. Study 19 was a multicenter, randomized, double-blind, placebo-controlled Phase 2 study of olaparib as a maintenance treatment for patients with PSR serous ovarian cancer. As with SOLO2, patients with PSR disease who were in response to their final platinum regimen and who had received at least two previous lines of platinum-based therapy were randomized to receive either olaparib or placebo. The primary endpoint of Study 19 was investigator assessed PFS. Study 19 was conducted with the capsule formulation of olaparib.

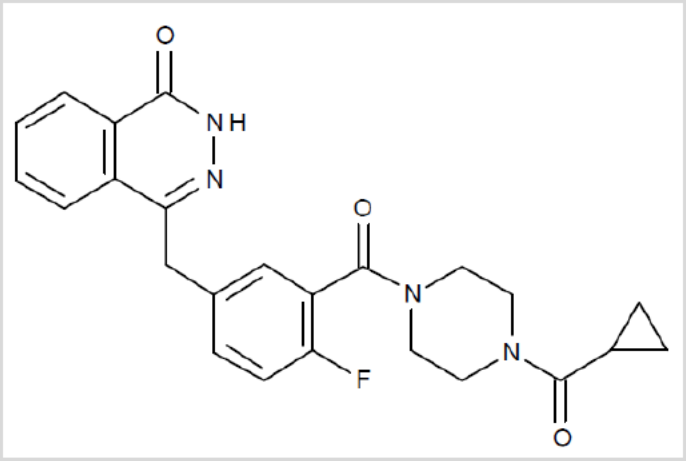
The approved dose for the capsule formulation of olaparib is 400 mg (8 x 50 mg capsules) taken twice daily (BID), equivalent to a total daily dose of 800 mg, administered until disease progression. In terms of convenience for patients, this dosing regimen is not optimal. The more patient-friendly tablet formulation of olaparib delivers a therapeutic dose in fewer dose units. (b) (4) . As a result, the capsule and tablet formulations are not interchangeable dose for dose and different monotherapy doses are recommended: 300 mg twice daily (BID) for the tablet formulation and 400 mg BID) for the capsule formulation.

While initial Phase 1 and Phase 2 clinical trials were conducted with capsules, the tablet formulation has been utilized across the entire olaparib Phase 3 program, including SOLO2. Following approval of the proposed NDA, two formulations of olaparib will be approved for use in ovarian cancer patients in the US that differ in terms of recommended total daily dose and unit strength. While the two formulations are distinctly different in terms of appearance and packaging, availability of both formulations in the marketplace creates the potential for

confusion. AstraZeneca is proposing a strategy for mitigating potential risk, a key component of which is to expedite removal of capsules from the US market.

In addition to standard CMC review, bridging of the capsule strengths to the proposed tablet regimen was a major review issue requiring coordination of biopharmaceutics, clinical pharmacology, DMEPA (labelling), and clinical. The two formulations were bridged through "A phase I , randomized, 2 period cross over study to determine the comparative bioavailability of thwo different oral formulations of AZD2281 in cancer patients with advanced solid tumors" (Study code: D0810C00024). This study compared the bioavailability of the (b) (4) tablet and the (b) (4) (capsule). Discussions with the clinical team and DMEPA resolved potential medication errors as a result of the change in dosing through labeling and presentation changes for the tablet formulation. This issue was resolved by better coordinating removal of the capsule formulation from the market; this was not a CMC review issue, but the CMC team does review the label and labeling. Review of post-marketing changes (b) (4) should be expedited to ensure continual supply of the tablet in this transition to minimize potential dosing errors from having both formulations available.

Olaparib is a selective, orally-available inhibitor of PARP (Poly (ADP-ribose) polymerase), (b) (4) Olaparib is "low solubility" as defined by the BCS system, (b) (4) . The partition coefficient for the drug substance between octanol and water at 25^{O}C is log P = 1.49. The drug substance is manufactured by (b) (4)



$C_{24}H_{23}FN_4O_3$
MW = 434.46 g/mol

CAS: 763113-22-0

IUPAC: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one

Laboratory Codes: AZD2281; KU-0059436

Olaparib is classified as genotoxic in accordance with the ICH guidance on 'Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (ICH S2 Guideline), having tested positive in Chinese Hamster Ovary (CHO) and in vivo rat bone marrow micronucleus assay. Therefore, AstraZeneca concludes that since olaparib is genotoxic, and as patients will have received multiple cycles of prior genotoxic chemotherapy, the control of potential genotoxic impurities to the threshold of toxicological concern (TTC) or the staged TTC is not considered appropriate in this context. This approach is consistent with the principles outlined in the ICH guidance on Assessment and Control of DNA Reactive (Mutagenic) Impurities in pharmaceuticals to Limit Potential Carcinogenic Risk (ICH M7 Guideline) and on Non-clinical Evaluation for Anticancer Pharmaceuticals (ICH S9 Guideline). Impurity specifications have been developed for all impurities above the ICH Q3A qualification threshold based on qualification in toxicology and/or clinical studies. The table below contains the comparison of the drug substance individual impurity limits in NDA 206-162 compared to NDA 208-558:

Organic impurities	Limit in NDA 206-162	Limit in NDA 208-558
(b) (4)		

(b) (4)

Comparison of drug product specifications:

(b) (4)

Olaparib 100 mg film-coated tablets are yellow to dark yellow, oval, bi-convex film-coated tablets, 145. X 7.25 mm, with debossment of "OP100" on one side and plane on the reverse.
Olaparib 150 mg film-coated tablets are green to green/grey, oval, bi-convex film-coated tablets, 14.5 x 7.25 mm, with debossment of "OP 150" on one side and plain on the reverse.

(b) (4)

The tablets are packaged in HDPE bottles with (b) (4) screw caps.

(b) (4)

NDA: 208558

Drug Product Name / Strength: Lynparza™ (olaparib) tablets, 100 and 150 mg

Route of Administration: Oral

Applicant Name: AstraZeneca Pharmaceuticals LP

Review Summary:

List Submissions being reviewed (table):

0000	**9-Dec-16**	**Original Submission**
0002	**22-Feb-17**	**Updated drug product stability data and labeling submissions**
0013	**5-Apr-17**	**Response to drug product and biopharmaceutics information requests**
0030	**1-Jun-17**	**Response to drug product information requests**

Highlight Key Outstanding Issues from Last Cycle: NA

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Olen Stephens

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Anamitro Banerjee

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LABELING

R Regional Information

1.14 Labeling

Immediate Container Label

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment: Adequate with comments.
The current labels include a section designated, "Area reserved for variable data". The applicant will be asked to confirm that this information will include expiry, NDC numbers, and lot data. The package insert was reviewed with the clinical division. The label includes adequate description of the two dose strengths to distinguish the two presentations in sections 3, 11, and 16. The highlights section is terse and describes the product as 100 mg and 150 mg tablets. Section 11 of the PI includes all excipients in the formulation and does not include promotional claims. Section 16 contains placeholders for the NDC number. The storage statements are supported by stability data, but does not exactly align with the definition of USP controlled room temperature. An information request was sent through the clinical division to align that definition.

Carton Labeling: NA

List of Deficiencies:

1. ***For the container closure labels, confirm that the area designated, "Area reserved for variable data" will contain lot number, NDC numbers, and expiry information.***

2. ***In the package insert in section 16 as well as on container labels, revise the storage statement to align with the definition of USP Controlled Room Temperature: "Store at 20^{O}C to 25^{O}C (68^{O}F to 77^{O}F), excursions permitted between 15^{O}C to 30^{O}C (59^{O}F to 86^{O}F) [see USP Controlled Room Temperature]. Store in original bottle to protect from moisture."***

The applicant has made the requested change in the package insert regarding the storage conditions, but changes to the container labels are still pending a response from the applicant. Review of the labels will be completed through negotiation with the applicant and the clinical division. From a labeling perspective, this NDA can be approved.

Primary Labeling Reviewer Name and Date: Olen M. Stephens 11-Jul-17

Secondary Reviewer Name and Date: Anamitro Banerjee 11-Jul-17

Olen Stephens

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Date: 7/11/2017 02:06:15PM
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Comments: Edits to the container label pending negotiation through the clinical division

Anamitro Banerjee

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NDA 208558

CHAPTER V: Process

PROCESS

Product Background: Olaparib is a selective, orally-available inhibitor of PARP (Poly (ADP-ribose) polymerase) (b) (4) Olaparib film-coated tablets are oral immediate release dosage forms which have been designed to be delivered in two individual dosage strengths, 100 and 150 mg, to achieve a nominal dose of 300 mg twice daily and to provide dose reduction options in 50 mg steps.

Olaparib is already available in the US as a 50 mg capsule (NDA application 206162, approved December 2014) and earlier (Phase 1 and 2) clinical trials predominantly used this capsule drug product. A tablet formulation has been designed to deliver the therapeutic dose of olaparib in fewer dose units than for capsule and this formulation has been used for the Phase III programme.

NDA: 208558

Drug Product Name / Strength: Olaparib Tablet/100 mg, 150 mg

Route of Administration: Oral

Applicant Name: ASTRAZENECA PHARMACEUTICALS LP

Review Summary:

Manufacturing process consists of (b) (4)

List Submissions being reviewed (Table):

208558.enx

Type of Document	Date of Document	Received date	Provision
Original	09-Dec-2016	09-Dec-2016	Original NDA
SD# 0022	04/21/2017	04/21/2017	Quality/Response to Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

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Hong Wen

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Daniel Obrzut

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FACILITIES

Product Background

NDA: 208558

Drug Product Name / Strength: Olaparib tablets; 100mg, 150mg

Route of Administration: Oral

Applicant Name: AstraZeneca Pharmaceuticals LP

Review Summary: All facilities in NDA 208558 are acceptable for the listed responsibilities

List Submissions being reviewed: NDA-208558-ORIG-1

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

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Steven Hertz

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Ruth Moore

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CHAPTER VII
BIOPHARMACEUTICS

Product Background:

NDA: 208558-ORIG-1

Drug Product Name / Strength: Olaparib film-coated tablets 100 mg, 150 mg

Route of Administration: Oral

Applicant Name: AstraZeneca

Background:

Olaparib was originally approved on Dec 19 2014 as a capsule formulation for the treatment of advanced ovarian cancer (NDA 206-162). As Olaparib capsules consist of 50 mg olaparib drug substance and the recommended dose of olaparib capsules is 400 mg bd po, patients are required to take 8 capsules bd, for a total of 16 capsules daily.
To improve convenience and reduce the pill burden for patients, the oral tablet formulation, the subject of the current NDA, was developed to deliver an efficacious dose of olaparib in fewer dosing units. Tablets contain 150 mg of olaparib, and the tablet dose is 300 mg po bd for a total of 4 tablets daily. To accommodate dose reductions, a 100 mg tablets have also been developed.

Submission:

The submission pertains to the Tablet formulation of Olaparib, which is a film-coated immediate release tablet to be delivered in two individual dosage strengths, 100 and 150 mg. (b) (4)

Review's Objective:

This Biopharmaceutics review is focused on evaluating the following:

- The proposed dissolution method
- The proposed dissolution acceptance criterion
- (b) (4)
-

Reviewer's Assessment:

The proposed dissolution method is adequate for quality control of the drug product. The proposed dissolution acceptance criteria are supported by the data provided and are acceptable. A

(b) (4)

The FDA-approved dissolution method as well as the acceptance criteria that were agreed to with the Applicant are as follows:

Dissolution Method	Apparatus	USP I
	Medium	50 mM pH 6.8 phosphate buffer
	Medium volume	900 mL
	Rotation speed	100 rpm
	Deaeration of medium	Yes
	Temperature in vessel	37 °C
	Analytical method	HPLC
Acceptance Criteria		100 mg: NLT (b) (4)% (Q) in 45 min 150 mg: NLT (b) (4)% in 30 min NLT (b) (4)% (Q) in 60 min

Conclusion and Recommendation:

From a Biopharmaceutics perspective, NDA 208558 for Olaparib film-coated tablets 100 mg, 150 mg is recommended for **APPROVAL.**

List of Submissions being reviewed (table):

eCTD #	Received date	Document
0000	12/09/2016	New NDA
0013	04/05/2017	Response to Information Request

Highlight of Key Outstanding Issues from Last Cycle: None. First review cycle.

Concise Description Outstanding Issues : None.

BCS Designation

Reviewer's Assessment:

Solubility: Olaparib does not exhibit pH dependent solubility and is is a 'low solubility' drug under the Biopharmaceutics Classification System (BCS) at the proposed dose. The solubility of olaparib ((b) (4) in a range of solvents is summarized in Table 1. (b) (4)

which increased the solubility of the drug substance in aqueous media.

Table 1. Solubility of olaparib (b) (4)

Solvent	Temperature (°C)	Solubility (mg/mL)	Solubility descriptive term
pH 4.5 Acetate Buffer	37	0.13	Very slightly soluble
pH 6.8 Phosphate Buffer	37	0.11	Very slightly soluble
0.1 M HCl	37	0.12	Very slightly soluble
Water	37	0.12	Very slightly soluble
Acetonitrile	20	3.1	Slightly soluble
Ethanol (99.5%)	20	5.5	Slightly soluble
Methanol	20	10.6	Sparingly soluble
Ethanol:water 75:25	20	19.7	Sparingly soluble
Methanol:water 50:50	20	3.5	Slightly soluble
DMF	20	48.0	Soluble

Permeability: Information is not provided in the submission.

Dissolution: See the section of "Dissolution Method and Acceptance Criteria" below.

Dissolution Method and Acceptance Criteria

Dissolution Method

The proposed dissolution method for olaparib film-coated tablets is as follows:

Apparatus	USP I
Medium	50 mM pH 6.8 phosphate buffer
Medium volume	900 mL
Rotation speed	100 rpm
Deaeration of medium	Yes
Temperature in vessel	37 °C
Analytical method	HPLC

Dissolution Method Development (\\CDSESUB1\evsprod\NDA208558\0000\m3\32-body-data\32p-drug-prod\active-film-coated-tablet-01\32p2-pharm-dev\pharmaceutical-development-attachment-1.pdf)

Three dissolution methods were developed and utilized in different stages of the drug product development (Table 2).

Table 2. Summary of Olaparib tablet dissolution methods used during development

Component	Method A	Method B	Method C
Application	(b) (4)		Proposed QC method, batch analysis
Dissolution medium			pH 6.8 buffer (0.05 M)
Volume (mL)			900
USP Apparatus			I, basket
Rotation speed			100
Comments			Operable and reproducible with clear discrimination of (b) (4) content

[a] Sodium dodecyl sulfate.

(b) (4)

Figure 1. In vitro dissolution profiles of olaparib 100 (left panel) and 150 mg (right panel) tablet formulation generated across the pH range of (b) (4) (USP I, 100 rpm, 37°C, 900 mL)

Dissolution volume in these investigations was limited to 900 mL to maximize solute capacity. Therefore, Method C was established to be USP-I, pH 6.8 buffer, 100 rpm, 900 mL.

Discriminating Ability of Method C:

To assess the discriminatory ability of the proposed dissolution methods, tablet variants were manufactured from the potential high risk failure models, such as:

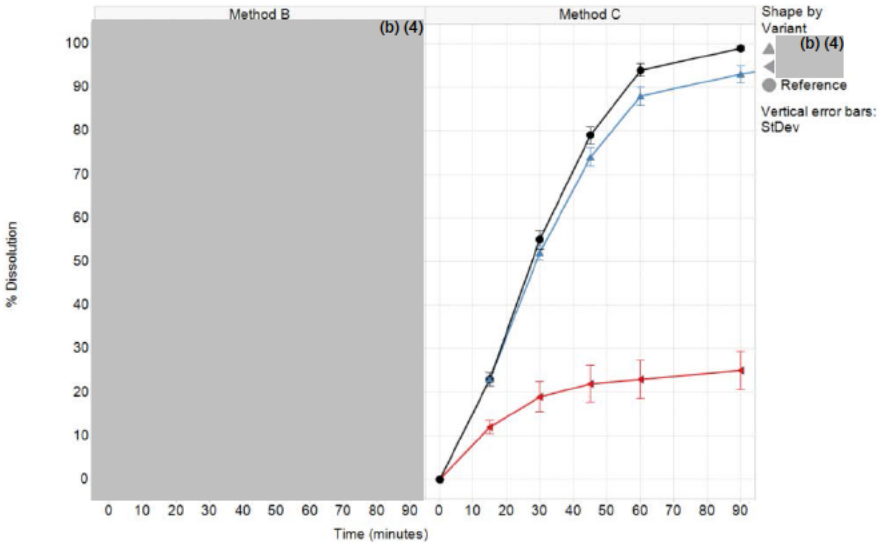

Figure 2. Dissolution profiles of olaparib 150 mg tablet variants, at the 6 month timepoint of the (b) (4) content stability study, comparing Methods B (left panel) and C (right panel)

Additional tablet variants with different levels of (b) (4) were manufactured and tested with Method C, and the results are shown in Figure 3. As the percentage of (b) (4) goes up, the dissolution rate of the proposed drug product goes down and incomplete dissolution was observed (b) (4)

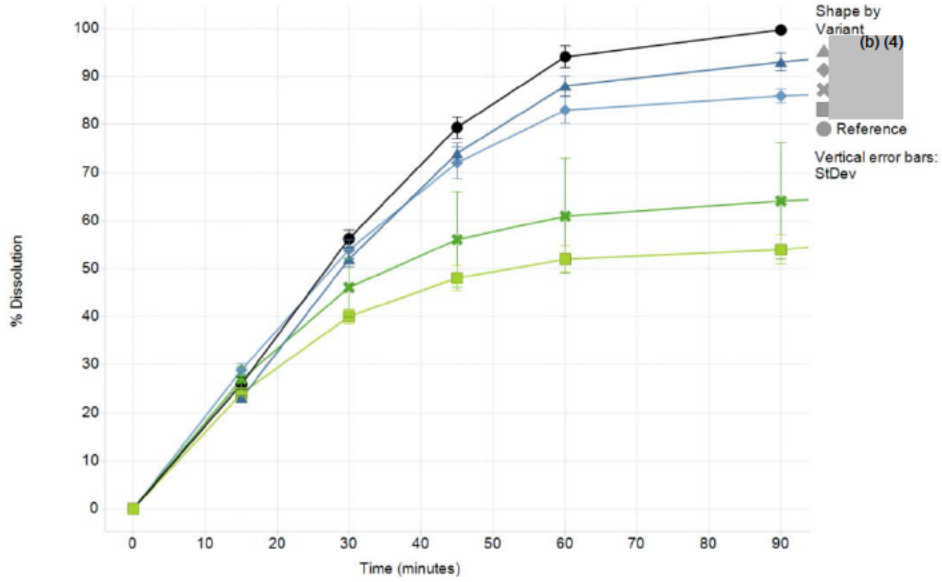

Figure 3. Dissolution profiles of the olaparib 150 mg tablet variants (b) (4), versus a control variant using Method C

Similar behavior was observed for the 100 mg tablet strength, with a decrease in rate and extent of dissolution (b) (4) (Figure 4).

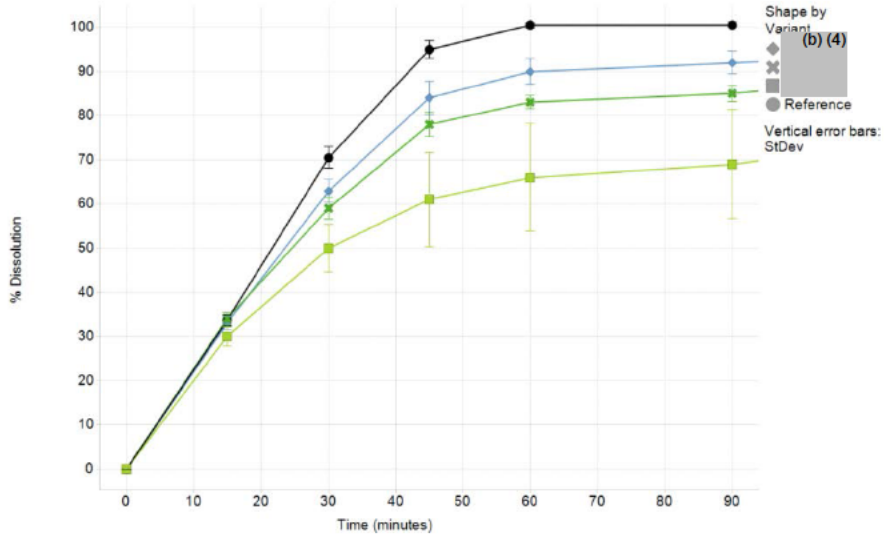

Figure 4. Dissolution profiles of the olaparib 100 mg tablet variants (b) (4) versus a control variant using Method C

Due to its ease of operability and enhanced discriminating ability (b) (4) Method C was selected as the QC method for the proposed drug product.

Reviewer's Assessment:

The dissolution method was optimized during the drug product development process. The final QC method (Method C) was demonstrated to be discriminating and operable. The method is adequate for quality control of the drug product.

It is noted that the dissolution test was the only proposed test to detect (b) (4) in the drug product due to its discriminating ability. The OPQ review team has requested verification of the robustness of the analytical methods by FDA/DPA labs, including the dissolution test itself and the analytical method by LC.

Dissolution Acceptance Criteria:

The initially proposed dissolution acceptance criteria are as follows:

- Q (b) (4) % at 45 min for the 100 mg tablet
- Q= (b) (4) % at 60 min for the 150 mg tablet

As recommended by FDA, the Applicant revised the acceptance criteria for the 150 mg Tablet to the following two-time-point criteria due to its slow dissolution.

NLT (b)(4)% in 30 min
NLT (b)(4)% (Q) in 60 min

The APPENDIX summarizes the Information Request comments conveyed to the Applicant on 03/24/2017; the Applicant's response was received on 04/05/2017.

The dissolution profiles of the batches for the 100 mg and 150 mg tablets are summarized in Figures 5 and 6, and in Table 3.

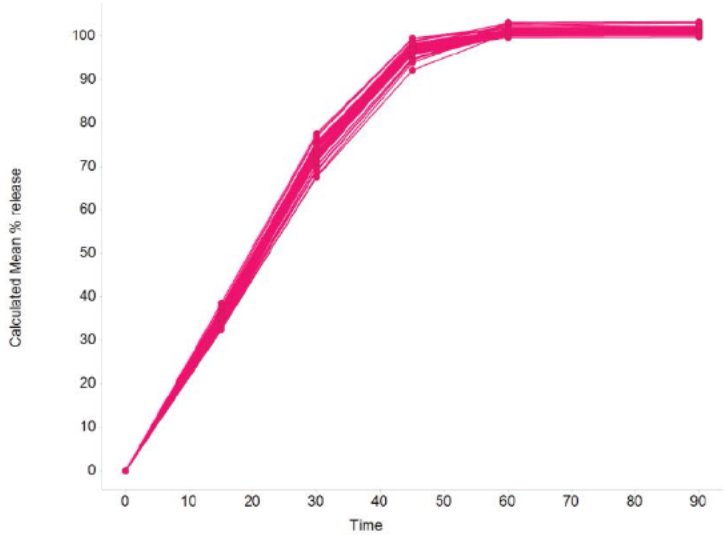

Figure 5. Batch dissolution profiles for 100 mg tablets

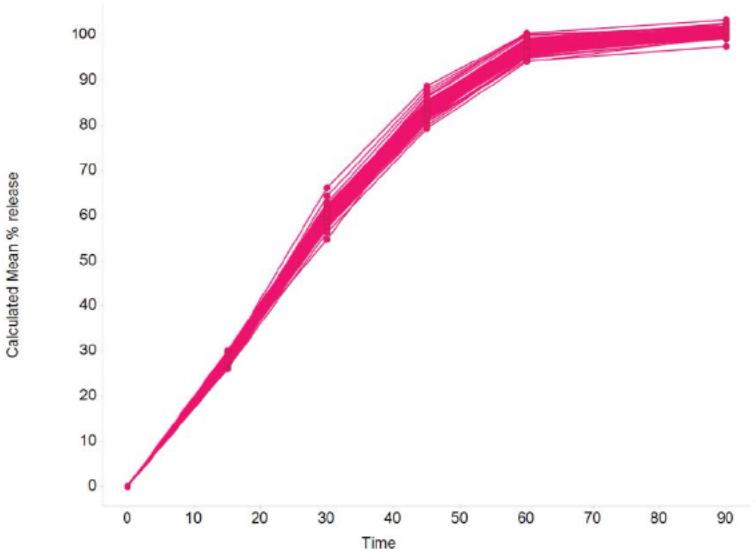

Figure 6. Batch dissolution profiles for 150 mg tablets

Table 3. Batch release dissolution results for olaparib 100 mg tablets (36 batches) and 150 mg tablets (90 batches)

	Results	15 min	30 min	45 min	60 min	90 min
100 mg	Overall mean	36	73	97	101	101
	SD of means	1.6	2.5	1.6	0.9	0.8
	Range of individual results	(b) (4)				
150 mg	Overall mean	28	60	84	97	101
	SD of means	1.0	1.5	1.6	1.3	0.9
	Range of individual results	(b) (4)				

The stability data shows no change in the dissolution performance of olaparib film-coated tablets when stored in HDPE bottles under both long term (25°C /60% RH for climatic zone I and II, 30°C /75% RH for climatic zone III and IV), and accelerated (40°C/75% RH) storage conditions. Therefore the same acceptance criteria are also proposed for shelf life specification.

Reviewer's Assessment:

The following proposed dissolution acceptance criterion for olaparib 100 mg tablets and the revised acceptance criteria for olaparib 150 mg tablets are supported by the dissolution data provided, and are acceptable.

100 mg: NLT (b) (4)% (Q) in 45 min
150 mg:
NLT (b) (4)% in 30 min
NLT % (Q) in 60 min

(b) (4)

(b) (4)

Bridging of Formulations

The pivotal Phase III Study D0816C00002 (SOLO2) which was designed to support the approval of the tablet formulation was conducted with the tablets of the proposed commercial formulation and manufactured at the commercial site and scale. Therefore, there is no bridging required between the clinical and commercial product.

Biowaiver Request

No biowaiver request was submitted in the NDA. Both the proposed strengths (100 mg and 150 mg) were used in the pivotal clinical trials to demonstrate efficacy and safety.

(b) (4)

(b) (4)

[redacted]

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:

Jing Li, Ph.D., 07/20/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Okpo Eradiri, Ph.D., 7/20/2017

APPENDIX

Biopharmaceutics Information Request Comments Sent on 03/24/2017 and Applicant Responses Received on 04/05/2017

Biopharmaceutics Comment #1

1. (b) (4)

The Applicant's Response:

The Applicant fully accepts the agency's position (b) (4) and stated that they do not intend to use (b) (4)

Biopharmaceutics IR Comment #2

2. *Please note that for poorly soluble drugs and slowly dissolving drug products, the selection of 2 time points for the setting of the dissolution acceptance criteria is appropriate. Based on the dissolution data provided, we recommend that you implement the following dissolution acceptance criteria for olaparib 150 mg tablets and provide the revised specifications table with the updated acceptance criterion for the dissolution test:*

   NLT (b) (4) *% in 30 min*
   Q= (b) (4) *% in 60 min*

The Applicant's Response:

The Applicant accepted the Agency's recommendation to implement the 2-timepoint acceptance criteria for olaparib 150 mg tablets. The updated Specifications table for olaparib, film-coated tablet, 150 mg was provided.

The Applicant's Responses are acceptable.

Jing
Li

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Okponanabofa
Eradiri

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Xiao Chen

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