CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209115Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 209115
Review #1

Drug Name/Dosage Form	Rubraca™ (Rucaparib) Tablets
Strength	200 mg and 300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Clovis Oncology
US agent, if applicable	Dr. Jeri Beltman

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
New NDA	6/23/2016	All including CMC
Quality Information	5/16/2016	CMC
Quality Information	7/5/2016	CMC
Quality Information	7/11/2016	CMC
Quality Information	7/12/2016	CMC
Quality Information	7/22/2016	CMC
Quality Information	8/3/2016	CMC
Quality Information	9/12/2016	CMC
Quality Information	9/23/2016	CMC
Quality Information	9/30/2016	CMC
Quality Information	10/11/2016	CMC
Quality Information	10/13/2016	CMC
Quality Information	10/21/2016	CMC
Quality Information	10/24/2016	CMC
Quality Information	10/26/2016	CMC
Quality Information	10/28/2016	CMC
Quality Information	10/7/2016	CMC
Quality Information	11/10/2016	CMC

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	CDER/OPQ/ONDP/DNDAPI
Drug Product	Xing Wang	CDER/OPQ/ONDP/DNDP 1
Process	Daniel Obrzut	CDER/OPQ/OPF/DPA 3
Microbiology	N/A	
Facility	Ruth Moore	CDER/OPQ/OPF/DIA/IABI
Biopharmaceutics	Jing Li (ONDP)	CDER/OPQ/ONDP/DBD
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI/ RBPMBI
Application Technical Lead	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP 1
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	Raanan Bloom	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) [redacted]	Type III	[redacted]	(b) (4) [redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.
[redacted]	Type III	[redacted]	[redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.
[redacted]	Type III	[redacted]	[redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.
[redacted]	Type III	[redacted]	[redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.
[redacted]	Type III	[redacted]	[redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.
[redacted]	Type III	[redacted]	[redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.
[redacted]	Type III	[redacted]	[redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.
[redacted]	Type III	[redacted]	[redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.
[redacted]	Type III	[redacted]	[redacted]	Adequate	Nov. 14, 2016	DMF not reviewed since sufficient information is in the NDA.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 106289		
IND (b) (4)		
IND (b) (4)		

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

Sufficient CMC information is provided to support approval of Rubraca™ (rucaparib) immediate release film-coated tablets. All review disciplines including drug substance, drug product, process, biopharmaceutics, facility, and EA recommended acceptable for the sections of the NDA they reviewed. There are no outstanding CMC deficiencies for the NDA. The overall recommendation for the facility evaluation is "Acceptable". Therefore, the NDA is recommended for **Approval** from the CMC standpoint.

II. Summary of Quality Assessments

A. Product Overview

Rucaparib is a NME drug developed for the treatment of advanced ovarian cancer. It is a potent, orally bioavailable small molecule inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2 and PARP-3. The drug substance, rucaparib camsylate, is manufactured by chemical synthesis. (b) (4) (b) (4) The drug product is an immediate release film coated tablets. It has a **24 months** of expiry when stored at 20°C to 25°C (68°F to 77°F).

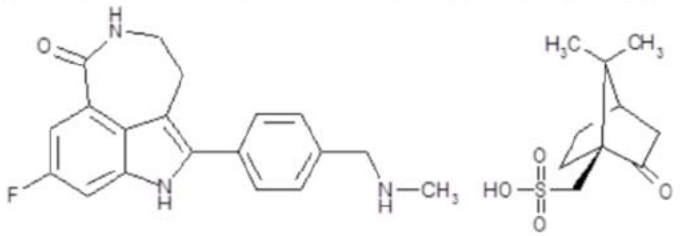
Proposed Indication(s) including Intended Patient Population	Monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA.
Duration of Treatment	Continue treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	1200 mg daily (600 mg orally twice daily)
Alternative Methods of Administration	N/A.

B. Quality Assessment Overview

Drug substance:
The drug substance, rucaparib camsylate, is a new molecular entity. It is a chemically synthesized, (b) (4) The drug substance will be used to manufacture an immediate release solid oral tablet. The drug product contains a (b) (4)

(b) (4) The indication is for the treatment of ovarian cancer patients with a deleterious BRCA-mutated tumor who have received 2 or more prior chemotherapy regimens.

Chemical Name and Structure: Rucaparib camsylate = 8-Fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid salt



Rucaparib is a non-hygroscopic, white to pale yellow powder. Rucaparib free base does not contain any chiral centers. Two chiral centers are present in the camphorsulfonic acid salt. (b) (4)

(b) (4)

Drug product:
Rubraca™ tablets have two dosage strengths of 200 mg and 300 mg (as active free base) that are (b) (4) The 200 mg tablet is 11 mm round convex, blue in color, and debossed with "C2" on one side. The 300 mg tablet is 8 mm × 16 mm oval, yellow in color, and debossed with "C3" on one side. The drug product contains (b) (4) rucaparib camsylate (b) (4) as the active ingredient and contains the following compendial excipients: microcrystalline cellulose (b) (4) and sodium starch glycolate (b) (4) colloidal silicon dioxide (b) (4) and magnesium stearate (b) (4) as the excipients. All excipients in the rucaparib tablets are compendial grade. The 200 mg tablets are coated with an OPADRY® II Blue coating system. The 300 mg tablets are coated with an OPADRY® II Yellow coating system. No overages are used in the drug product.

Excipients are selected based drug substance physicochemical properties, drug load and intended manufacturing process (b) (4) Three formulation variables that may impact product Critical drug product attributes (CQAs) most were identified as drug load, (b) (4) because of their

potential to impact compaction, compression and dissolution. Rucaparib tablet formulations have used the same drug substance and excipients throughout clinical development (b) (4)

The drug product release specification consists of the following test attributes: appearance, identity, assay, degradation products, dissolution, uniformity of dosage units, (b) (4) and microbial limits. The proposed drug product specification is deemed adequate to assure identity, strength, purity, and quality of the drug product.

The commercial container closure system of the drug product is 200 mg / 60 counts in 60 cc HDPE bottle (b) (4), and induction seal liner; and 300 mg / 60 counts in 120 cc HDPE bottle (b) (4) and induction seal liner.

The applicant provided 6-month accelerated and 12-month long term stability results from six primary stability batches manufactured at the development site (b) (4) The applicant also provided 3 months accelerated stability data from one batch of each strength manufactured at the commercial site (b) (4) Based on the review of the stability data, the proposed expiration period of **24 months** is granted for the drug product when packaged in the proposed packaging configuration and stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Process:
The manufacturing process has essentially remained the same throughout clinical development and the manufacture of the primary stability batches used in the primary stability studies. The process also remains the same for commercial manufacturing. The manufacturing process consists (b) (4). (b) (4) (b) (4) The process involves the following unit operations:

(b) (4)

Rationale for choosing appropriate unit operations and process parameters was provided and found to acceptable. How the process will affect the physicochemical stability of the drug substance was studied. The applicant has discussed potential impact of each unit operations on pertinent quality attributes and identified potential high risk steps (see 3.2.P.2.3-1). The overall conclusion for risk assessment for the unit operations on CQAs

is either low to medium risk. In-process and batch analysis data from multiple clinical batches manufactured using the proposed commercial process near commercial batch size demonstrate that the proposed commercial process and control strategy consistently yield drug product that meets the Quality Target Product Profile.

Facility:
There is one drug substance manufacturing facility (b) (4) that is responsible for drug substance manufacturing, controls and testing. The facility is not recommended for preapproval inspection (PAI) after evaluation its profile and GMP inspection history. The facility is deemed acceptable.

There are three drug product manufacturing and testing facilities (b) (4) All three facilities are not recommended for PAI after evaluation its profile and GMP inspection history. All the facilities are deemed acceptable.

Overall, the manufacturing and controls facilities for both drug substance and drug product are found to be acceptable.

Biopharmaceutics:
Rucaparib tablet is an immediate release film-coated tablet for oral administration. The proposed dissolution method was adequately justified. The revised dissolution acceptance criterion is supported by the dissolution data provided and is acceptable.

The proposed commercial formulation and the clinical trial formulation are adequately bridged by the dissolution data and in vivo PK studies.

The comparability protocol was reviewed and found acceptable.

NDA 209115 for Rucaparib tablets, 200mg and 300mg, is recommended for APPROVAL from a Biopharmaceutics perspective. The approved dissolution method and acceptance criterion for Rucaparib tablets, 200mg and 300mg, are as follows:

Apparatus	USP Apparatus 2 (paddle)
Speed	75 rpm
Medium	0.01 N hydrochloric acid (HCl)
Volume	900 mL
Temperature	37°C
Acceptance Criterion	Q= (b) (4) % at 15 min

Environmental Analysis:
The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. FDA requested additional information due to the status of the active ingredient as a new molecular entity (NME) and the potential for

hormonal activity, per recent FDA guidance. The claim and supporting information were reviewed and the claim found to be acceptable.

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.
18-Nov-2016

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CHAPTER IV: Labeling

Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

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

Rubraca™ (rucaparib) tablets, for oral use
Initial U.S. Approval: YYYY

----------INDICATIONS AND USAGE----------

Rubraca is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy treatment of (b) (4) patients with deleterious BRCA (b) (4) (b) (4)

This indication is approved under accelerated approval based on (b) (4) response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose is 600 mg orally twice daily. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 200 mg and 300 mg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): MDS/AML occurred in patients exposed to Rubraca, including one fatal event of AML. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed. (5.1)
- Embryofetal toxicity: Rubraca can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (≥ 20%) were nausea, fatigue (including asthenia), vomiting, anemia, dysgeusia, decreased appetite, diarrhea, thrombocytopenia, dyspnea. (6.1)
- Most common laboratory abnormalities were increase in creatinine, increase in ALT, increase in AST, decrease in hemoglobin, decrease in lymphocytes, increase in cholesterol, decrease in platelets, decrease in absolute neutrophil count. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Clovis Oncology, Inc. at 1-844-258-7662 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: (b) (4) (8.2)

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

Revised: M/YYYY

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name: Rubraca™ Established name: rucaparib	Adequate
Dosage form, route of administration	Dosage: Tablet Route: Oral	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 200 mg and 300 mg	Adequate

Conclusion: Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Tablets (200 mg): blue, round, immediate-release, film-coated, debossed with "C2".

Tablets (300 mg): yellow, oval, immediate-release, film-coated, debossed with "C3".

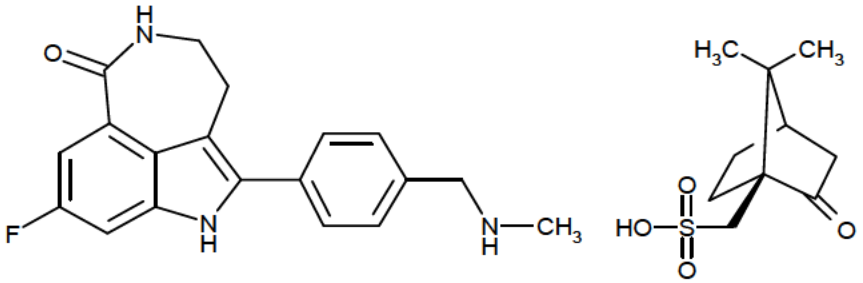
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Adequate
Strengths: in metric system	200 mg and 300 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Tablets (200 mg): blue, round, immediate-release, film-coated, debossed with "C2". Tablets (300 mg): yellow, oval, immediate-release, film-coated, debossed with "C3".	Adequate

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

Rucaparib is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme. The chemical name is 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid salt. The chemical formula of rucaparib camsylate is $C_{19}H_{18}FN_3O \cdot C_{10}H_{16}O_4S$ and the relative molecular mass is 555.67 Daltons.

The chemical structure of rucaparib camsylate is shown below:



Rucaparib camsylate is a white to pale yellow powder; formulated into a tablet for oral dosing. Rucaparib shows pH-independent low solubility of approximately 1 mg/mL across the physiological pH range.

Rubraca (rucaparib) tablets contain rucaparib camsylate as the active ingredient. Each 200 mg tablet contains 344 mg rucaparib camsylate equivalent to 200 mg rucaparib free base. Each 300 mg tablet contains 516 mg rucaparib camsylate equivalent to 300 mg rucaparib free base.

The inactive ingredients in Rubraca tablets include: microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate. The cosmetic blue film coating for 200 mg tablets and cosmetic yellow film coating for 300 mg tablets is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, and talc. The coating is colorized as blue using brilliant blue aluminum lake and indigo carmine aluminum lake, or yellow using yellow iron oxide.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Provided	Adequate
Dosage form and route of administration	Provided	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Provided	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	Adequate

Conclusion:

Miss "salt" in the chemical name. Added in the labeling. Adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16.1 How Supplied

Rubraca is available as 200 mg and 300 mg tablets.

200 mg Tablets:

- Blue, round, and debossed with "C2" on one side
- Supplied in bottles of 60 tablets (NDC: 69660-201-91)

300 mg Tablets:

- Yellow, oval, and debossed with "C3" on one side
- Supplied in bottles of 60 tablets (NDC: 69660-203-91)

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Provided	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 60 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Provided	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Clovis Oncology, Inc. Boulder, CO 80301 1-844-258-7662	Adequate

Conclusion:
The following comment was conveyed to the Firm on 02-Nov-2016:
Change the storage conditions of rucaparib tablets (200 mg and 300 mg) in the Package Insert (16.2) and Container Labels to: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Firm has made the changes. Acceptable.

R Regional Information

1.14 Labeling

Immediate Container Label

(b) (4)

[redacted]

Reviewer's Assessment:
Acceptable.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Rubraca™ (rucaparib) tablets	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided. Salt equivalency statement is provided.	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral use	Adequate
Net contents* (21 CFR 201.51(a))	60 tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not required for an oral dosage form	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provide	Adequate
"Rx only" statement per 21 CFR	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate
Others	Keep out of the reach of children	Adequate

* 21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
** For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
** Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements..

Carton Labeling

No carton labeling is provided.

Reviewer's Assessment:
N/A

List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Xing Wang, Ph.D., 03-Nov-2016

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

Anamitro Banerjee, Ph.D., ONDPI/NDPBII Acting Branch Chief,

Anamitro Banerjee

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Xing Wang

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BIOPHARMACEUTICS

Product Background:

NDA 209115

Drug Product Name / Strength: Rucaparib Tablets, 200 mg and 300 mg

Route of Administration: Oral

Applicant Name: Clovis Oncology

Review Summary:

Rucaparib tablet is an immediate release film-coated tablet for oral administration. The proposed dissolution method was adequately justified. The revised dissolution acceptance criterion is supported by the dissolution data provided and is acceptable.
The proposed commercial formulation and the clinical trial formulation are adequately bridged by the dissolution data and in vivo PK studies.
The comparability protocol was reviewed and found acceptable.

NDA 209115 for Rucaparib tablets, 200mg and 300mg, is recommended for APPROVAL from a Biopharmaceutics perspective. The approved dissolution method and acceptance criterion for Rucaparib tablets, 200mg and 300mg, are as follows:

Apparatus	USP Apparatus 2 (paddle)
Speed	75 rpm
Medium	0.01 N hydrochloric acid (HCl)
Volume	900 mL
Temperature	37ºC
Acceptance Criterion	Q= (b) (4) at 15 min

List of Submissions reviewed:

eCTD #	Received date	Document
0001	5/16/2016	Multiple categories
0004	7/05/2016	Quality/ Response to Information Request
0006	7/11/2016	Quality/ Response to Information Request
0007	7/12/2016	Quality/ Response to Information Request
0008	7/22/2016	Quality/ Response to Information Request
0009	7/22/2016	Quality/ Response to Information Request
0011	8/3/2016	Quality/ Response to Information Request (comparability protocol)

0022	9/12/2016	Quality/ Response to Information Request
0025	9/23/2016	Quality/ Response to Information Request
0039	10/24/2016	Quality/ Response to Information Request

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

Concise Description of Outstanding Issues: None.

BCS Designation

Reviewer's Assessment: The Applicant did not request BCS classification in the Application. The proposed drug product is considered highly soluble in the pH range of 3.2 to 7.6, but the solubility is low in pH 1.2.

Solubility: (b) (4)

Table 1. Solubility of Rucaparib

(b) (4)

Permeability: Information is not provided in this Application.

Dissolution: Please see the section below.

Dissolution Method and Acceptance Criteria

The proposed dissolution method is summarized in the table below:

Table 2. The proposed dissolution method for Rucaparib Tablets

Apparatus	USP Apparatus 2 (paddle)
Speed	75 rpm
Medium	0.01 N hydrochloric acid (HCl)
Volume	900 mL
Temperature	37ºC
Analytics	UV spectroscopy

The dissolution method was selected based on the following developmental studies.

Drug solubility in various dissolution media

(b) (4)

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(b) (4)

The dissolution profiles are consistent with an immediate release formulation.

Reviewer's Assessment:

The rucaparib tablet is an immediate release film-coated tablet for oral administration. The Applicant proposed the following dissolution method for quality control:

Apparatus	USP Apparatus 2 (paddle)
Speed	75 rpm
Medium	0.01 N hydrochloric acid (HCl)
Volume	900 mL
Temperature	37ºC
Analytics	UV spectroscopy

☐ The selection of apparatus, speed, and media have been adequately justified.

(b) (4)

The proposed dissolution method is ADEQUATE for the purpose of quality control of the drug product.

Dissolution Acceptance Criterion:

Based on drug release profiles obtained for drug product batches utilized for clinical investigation and primary stability studies, the Applicant proposed an acceptance criterion of Q = (b) (4)% at (b) (4) minutes. However, the data support a tighter acceptance criterion of Q = (b) (4)% at 15 min, as shown in the plots below for the clinical batches and the primary stability batches. The clinical batches include the commercial formulation (Formulation E 200mg and 300mg), (b) (4)

(b) (4)

Figure 4. Dissolution profiles of the clinical batches at release (reviewer's plot)

(b) (4)

Figurer 5. Dissolution at the 15-min time point during long term stability (reviewer's plot)

Reviewer's Assessment:

The provided dissolution data support a dissolution acceptance criterion of "Q = (b) (4) % at 15 min". The Applicant will be requested to revise the acceptance criterion.

The following IR comment was conveyed to the Applicant on 11 October 2016:

The proposed dissolution acceptance criterion of "Q = 80% at (b) (4) min" is not acceptable, and the dissolution data provided support a tighter acceptance criterion of "Q = (b) (4) % at 15

min". Implement the recommended dissolution acceptance criterion for your proposed product and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

In the IR response received on 24 October 2016, The Applicant accepted FDA's recommendation and revised the acceptance criterion to "Q= (b) (4)% at 15 min". The updated drug product specifications table has been submitted. The response is acceptable.

Reviewer's Assessment:

The revised acceptance criterion of "Q= (b) (4)% at 15 min" is acceptable.

Bridging of Formulations

A total of five formulations were used in clinical development. (b) (4) (b) (4)

Table 7. Summary of Rucaparib Formulations, Changes Made and Rationale

Formulation	Use in Clinical Study	Dosage Form Strength(s)	Drug Load (%w/w)	Excipients in Final Drug Product	Process[1]	Changes and Rationale
(b) (4)						
E	CO-338-010 CO-338-017	Film-Coated Tablet, 200 mg and 300 mg	73.7 (rucaparib camsylate)	Microcrystalline cellulose, sodium starch glycolate, colloidal silicone dioxide, magnesium stearate, Opadry II blue (200 mg), Opadry II yellow (300 mg)		

(b) (4)

(b) (4)

(b) (4) FDA recommended acceptance criterion of "Q =(b) (4)% at 15 min". In addition, the Office of Clinical Pharmacology determined that the pharmacokinetics of all formulations are (b) (4) based on the population PK analysis, which also supports the bridging across the formulations.[1]

Reviewer's Assessment:

Though a few formulations have been developed and used in the clinical studies, the proposed commercial formulation (Formulation E) was introduced in a phase 1/2 study and used since then. The proposed commercial formulation was adequately bridged to the clinical formulations by in vivo PK studies based on OCP analysis.

Biowaiver Request

A biowaiver request was submitted for the 200mg strength, (b) (4) (b) (4) (b) (4) (b) (4) Rucaparib tablets (200 mg & 300 mg) are manufactured (b) (4) and have the same manufacturer (b) (4) The dissolution profiles of both strengths are comparable as shown in Figure 4 (Formulation E).

Reviewer's Assessment:

(b) (4) (b) (4) (b) (4) Therefore the biowaiver request for the 200mg is granted.

R Regional Information

Comparability Protocols

(b) (4)

[1] Meeting minutes for IND106289 dated 4/15/2016.

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ENVIRONMENTAL ANALYSIS

[Suggested exec. summary: The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. FDA requested additional information due to the status of the active ingredient as a new molecular entity (NME) and the potential for hormonal activity, per recent FDA guidance. The claim and supporting information were reviewed and the claim found to be acceptable.]

R Regional Information

Environmental Analysis

Rucaparib is a small molecule inhibitor of poly-ADP ribose polymerase (PARP) currently being developed by the applicant as an oral monotherapy for patients (b) (4) ovarian cancer who have been identified as having a BRCA (b) (4) mutation on analysis of tumor tissue deoxyribonucleic acid (DNA).

The applicant noted in a written submission for a November 2, 2015 Type B meeting during the investigational new drug (IND) phase (IND 106289) that, based on current market projections, the maximum annual production of rucaparib for all dosage forms in the next 5 years will be approximately (b) (4) which converts to an expected introduction concentration (EIC) of approximately (b) (4) ppb. The applicant asked whether FDA agreed that this concentration would qualify the NDA for a categorical exclusion from an environmental assessment (EA). FDA responded that while the NDA would appear to qualify for the exclusion based on 21 CFR 25.31(b) (for drugs that increase in use but have an EIC less than 1 ppb), the data from a nonclinical embryo-fetal development toxicology study of rucaparib in rats, combined with the relatively high production volume, raised questions about rucaparib residues in the environment and potential toxicity to environmental organisms. Thus, additional information would be needed before FDA could make the determination regarding the exclusion. FDA also highlighted the recently published (at the time) draft environmental guidance related to drugs with potential estrogenic, androgenic, or thyroid hormone pathway activity (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf).

During the Type B meeting, the applicant responded with information regarding rucapirab's structure, receptor screening assays, nonclinical toxicology, and production data. The applicant argued that recapirab's structure is distinct from that of estrogen, progesterone, androgen, and triiodothyronine, and that there was a lack of significant androgenic and estrogenic receptor inhibition. FDA responded that other structures could still have estrogenic, androgenic, or

thyroid effects, but that such information, along with the data on the receptor binding values, a literature search about non-involvement in the estrogentic, androgenic, and thyroid pathways, and any available data on the potential environmental effects of other PARP inhibitors, would be useful in supporting the exclusion claim. The applicant agreed to provide this information with the NDA.

For the NDA, the applicant requested a claim for a categorical exclusion from an EA, per 21 CFR 25.31(b). The applicant provided a calculation for this concentration to support this claim, noting that the (b) (4) ppb EIC was developed based on the assumption that all drug products produced in a year are used and enter the publicly owned treatment works system, drug product usage occurs throughout the United States in proportion to the population and amount of waste water generated, and there is no metabolism. The applicant also provided a statement that to their knowledge, no extraordinary circumstances exist.

The applicant responded to FDA's request for additional information to support the EA exclusion claim by providing a report, Summary of Pharmacologic and Toxicological Properties. This report provided the following information.

1. The chemical structure of rucaparib does not contain a steroid backbone and is distinct from estrogen, progesterone, androgen, and triiodothyronine.

2. Quantitative structure-activity relationship (QSAR) model analysis of the rucaparib structure using the deductive estimation of risk from existing knowledge base (DEREK, Lhasa Limited) did not issue an alert relating to relevant endocrine endpoints including adrenal gland, estrogenicity, testicular and thyroid toxicity, although the applicant acknowledged that given the diverse nature of molecules that may elicit endocrine-related drug toxicity, structure-based approaches are limited in describing and predicting the in vivo effects of a given drug.

3. Receptor inhibition assays that were conducted on endocrine receptors found no significant inhibition (> (b) (4)%) of these receptors at a (b) (4) µM concentration of rucaparib, which was approximately (b) (4) fold (b) (4) than the Cmax unbound plasma rucaparib concentration ((b) (4) µM) observed in patients at 600 mg BID.

4. There were no anatomic pathology findings in any of the organs related to the endocrine system other than the thymus in rat and dog after multiple doses of rucaparib. However, effects on the lymphopoietic system noted with rucaparib were not confined to the thymus.

5. In clinic studies of oral rucaparib to date, including 433 patients treated with rucaparib (600 mg BID, the recommended dose) no hormonally driven adverse events have been reported that would suggest a modulation of the endocrine system by rucaparib.

6. Published studies suggested that there is evidence that PARP-1 and/or PARP-2 may play a role in estrogen, androgen, and thyroid signaling, but that results from a comprehensive toxicology program on rucaparib, described below, provides no evidence to support that the mechanisms proposed have translational relevance in vivo.

The applicant concluded that based on this information, it is unlikely that rucaparib modulates the endocrine system and thus no extraordinary circumstances are associated with rucaparib.

Reviewer's Assessment:

The categorical exclusion claim is appropriate for the anticipated amount of drug to be used, the calculation appears accurate, and an adequate statement of no extraordinary circumstances is present. The data provided by the applicant support the claim for the categorical exclusion from an EA, (b) (4) (2) some of the literature providing evidence that PARP-1 and/or PARP-2 may play a role in estrogen, androgen, and thyroid signaling. While these results are countered by the toxicology and other data indicating that there is no translational relevance in vivo, FDA also conducted a supporting fish plasma model (FPM) assessment to assess whether the EIC would result in fish plasma levels similar to human therapeutic plasma levels, per Huggett et al. (2003):

Fish Plasma Model (Huggett et al., 2003)	Comments

The results of this model is that the fish plasma concentration for recaparib would be (b) (4) times lower than the human therapeutic level, which provides additional support to the claim

for the categorical exclusion, especially given the conservative assumptions used for estimating the EIC.

The claim for a categorical exclusion from an EA is acceptable.

References:

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). "A Theoretical Model for Utilizing Mammalian Pharmacology and Safety Data to Prioritize Potential Impacts of Human Pharmaceuticals to Fish." Human and Ecological Risk Assessment: An International Journal 9(7): 1789-1799.

Scott, W. C., Du, B., Haddad, S. P., Breed, C. S., Saari, G. N., Kelly, M., ... & Brooks, B. W. (2016). Predicted and observed therapeutic dose exceedances of ionizable pharmaceuticals in fish plasma from urban coastal systems. Environmental Toxicology and Chemistry, 35(4), 983-995.

Tanoue, R., Nomiyama, K., Nakamura, H., Kim, J. W., Isobe, T., Shinohara, R., ... & Tanabe, S. (2015). Uptake and tissue distribution of pharmaceuticals and personal care products in wild fish from treated-wastewater-impacted streams. Environmental science & technology, 49(19), 11649-11658. doi: 10.1021/acs.est.5b02478

Primary EA Reviewer Name and Date: Jim Laurenson, 11/16/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, 11/16/2016

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James Laurenson

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