

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207970Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	207970		
Applicant Name	ACTAVIS LLC		
Drug Product Name	Cabazitaxel		
Dosage Form.	Injection		
Proposed Strength(s)	60 mg/6 mL (10 mg/mL).		
Route of Administration	Intravenous		
Maximum Daily Dose	25 mg/m ²		
Rx/OTC Dispensed	Rx		
Proposed Indication	Cabazitaxel Injection is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.		
Drug Product Description	Cabazitaxel Injection is supplied in single-dose, (b) (4) glass vials, as a clear, oily, light yellow solution, without macroscopic particles in suspension containing cabazitaxel 10 mg/mL (solvent free) in the following package strength: Cabazitaxel Injection 60 mg/6 mL (10 mg/mL)		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature]. Note: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.		
Review Team	Discipline	Primary	Secondary



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Template Revision: 03

	<i>Drug Substance</i>	Rajan Pragani	Haripada Sarker
	<i>Drug Product/ Labeling</i>	Tefsit Bekele	Xing Wang
	<i>Manufacturing</i>	Jinong Jenn Li	Kshitij Patkar
	<i>Microbiology</i>	Hemlata Tamta	Denise Miller
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Utkarsh Desai	
	<i>ATL</i>	Xing Wang	
Consults	None		

2. Final Overall Recommendation - Approval

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Cabazitaxel Injection, 10 mg/mL (60 mg/6 mL (b) (4)) was tentatively approved on January 07, 2018. On September 21, 2023 the applicant, Actavis LLC, an indirect, wholly owned subsidiary of Teva Pharmaceuticals USA, Inc submitted a Class II resubmission to request final approval. The following major changes are included in the resubmission:

- *Withdraw the tentatively approved Cabazitaxel drug substance DMF (b) (4) manufactured by (b) (4) (b) (4)*
- *Propose new Cabazitaxel Drug Substance, DMF (b) (4), manufactured by (b) (4)*



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*Overall, the applicant has provided sufficient information in this resubmission to assure the identity, strength, purity, and quality of the proposed drug product. Manufacturing processes, facilities and microbiology sections were adequate in last round review and remain acceptable (NAI). Based on the OPQ review team's evaluation of the information provided in the resubmission, OPQ recommends **APPROVAL of NDA 207970, CABAZITAXEL injection, for intravenous use.***

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - N/A
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments: None



Xing
Wang

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	N/A	
Established name(s)	Cabazitaxel injection	Adequate
Route(s) of administration	Intravenous	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Change to Injection: 60 mg/6 mL (10 mg/mL) solution in single-dose vial
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	(b) (4)	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4)	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	Adequate
Strength(s) in metric system	(b) (4)	Change to the following to only include dosage form, strength, physical characteristics of the product and packaging type. Injection: 60 mg/1 mL (10 mg/mL) as a clear, oily, light-yellow solution in single-dose vial
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Provided as shown above	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not provided	Recommendation is shown above

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Proprietary name: N/A Established name: Cabazitaxel	Adequate
Dosage form(s) and route(s) of administration	Injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	Change to Cabazitaxel Injection is a sterile, non-pyrogenic, preservative-free, clear, oily light yellow solution and is available in single-dose vial containing 60 mg/6 mL (10 mg/mL) cabazitaxel for intravenous use. Each mL contains 10 mg cabazitaxel (non-solvate), citric acid anhydrous (3 mg), ethanol (23%v/v), polysorbate 80 (260 mg) and polyethylene glycol 400 (585.28 mg).
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	See above	See above

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	(b) (4)	See above (the applicant agreed to report EtOH content in volume as 23%v/v)
Pharmacological/therapeutic class	antineoplastic agent belonging to the taxane class	Adequate
Chemical name, structural formula, molecular weight	(b) (4)	Change to Molecular weight: 896.03 (for the 2-propanol solvate) / 835.93 (for non-solvate).
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Injection	Adequate

Strength(s) in metric system	60 mg/6 mL	Adequate
Available units (e.g., bottles of 100 tablets)	(b) (4)	Change to NDC 0591-3038-20 Cabazitaxel Injection 60 mg/6 mL (10 mg/mL) in a carton
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Change to Cabazitaxel Injection is supplied as a clear, oily, light-yellow solution in single-dose vial in the following package strength:
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not provided	See above for recommendation
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size	N/A	

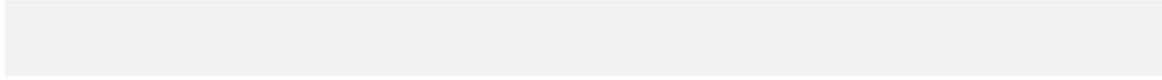
and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4)	Change to Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Manufactured In Romania By: Sindan Pharma SRL Bucharest 1, Romania 011171 Manufactured for: Teva Pharmaceuticals Parsippany, NJ 07054 USA	Adequate

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling is adequate from the product quality perspective.



3.0 CARTON AND CONTAINER LABELING

3.1 Container Label



3.2 Carton labeling N/A

Item	Information Provided in the NDA	Assessor's Comments about Container Label
Proprietary name, established name, and dosage form (font size and prominence)	Proprietary name: Established name: cabazitaxel	Adequate
Dosage strength	60 mg/6 mL (10 mg/mL)	Adequate
Route of administration	For intravenous infusion only	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	Adequate
Net contents (e.g. tablet count)	6 mL	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Ethanol (23% v/v)	Adequate
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Container Label
Name of manufacturer/distributor	Mfd. In Romania For: Teva Pharmaceuticals Parsippany, NJ 07054	Adequate
Medication Guide (if applicable)	N/A	-
No text on Ferrule and Cap overseas	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Container Labels: Adequate

The latest container label submitted is acceptable from the CMC perspective. The following information request regarding the carton labeling will be sent to the applicant.

1. On the carton labeling change [REDACTED] (b) (4) [REDACTED] to “Each mL contains: 10 mg cabazitaxel, citric acid...”

Overall Assessment and Recommendation:

The container label, carton labeling and prescribing information comply with all regulatory requirements, and they are recommended for approval from a CMC perspective pending revision of what are noted in the Assessor's Comments column and the information request above.

Primary Labeling Assessor Name and Date: Tefsit Bekele February 20, 2024

Secondary Labeling Assessor Name and Date David Claffey February 20, 2024



TEFSIT
BEKELE

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David
Claffey

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Date: 2/20/2024 05:42:08PM

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/s/

XING WANG
02/26/2024 10:01:30 AM

Recommendation: Approval

**NDA 207970
Review #2**

Drug Name/Dosage Form	Cabazitaxel Injection
Strength	10 mg/mL ((b) (4) 60 mg/6 mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Actavis LLC (an indirect, wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc.)
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission NDA 0001	11/2/2017	DS/DP/Process/Microbiology/Facility
Quality Amendment 0014	11/15/2017	DS/DP/Process/Microbiology

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
Drug Product	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
Process	Daniel Obrzut	CDER/OPQ/OPF/DPA1
Facility	Derek Smith	CDER/OPQ/OPF/DIA
Microbiology	Christine Craig	CDER/OPQ/OPF/DMA
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI
Application Technical Lead (ATL)	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
ORA	N/A	
Environmental Analysis (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA-207920 was tentatively approved on 8/24/2015 and was resubmitted on 11/02/2017. The CMC information in the resubmission remains unchanged except some updated information for commercial batch size and analytical methods for the drug substance, drug product, and excipients. The updated CMC information in the resubmission has been reviewed and found Acceptable. The NDA is recommended for Approval from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Cabazitaxel is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	Cabazitaxel Injection 20 mg/m ² administered every three weeks as a one-hour intravenous infusion in combination with oral prednisone 10 mg administered daily throughout Cabazitaxel Injection treatment. A dose of 25 mg/m ² can be used in select patients at the discretion of the treating healthcare provider
Alternative Methods of Administration	None.

B. Quality Assessment Overview

Chemical Name and Structure:



(b) (4)

Cabazitaxel is a white or off-white powder. It is freely soluble in dichloromethane, soluble in absolute ethanol and insoluble in water. (b) (4)

Cabazitaxel exhibits polymorphism. There are 18 known solid forms reported in the literature. (b) (4)

Cabazitaxel Injection is provided as 10 mg/mL ((b) (4) 60 mg/6 mL) sterile solution for intravenous infusion, which is similar to the listed drug, *JEVTANA (cabazitaxel) Injection*. The differences between the LD and the proposed Cabazitaxel Injection are the strength (LD is provided as 60 mg/1.5 mL solution) and the excipients used in the drug product formulations.

The original NDA (207920) was submitted on 10/23/2014 and was tentatively approved on 8/24/2015. The resubmission dated 11/02/2017 seeks full approval of the NDA. The CMC information remains mostly unchanged from the original NDA except the following changes: 1) commercial batch record for the drug product; 2) excipient specifications; and 3) analytical methods for the drug substance and drug product specifications. The resubmission contains the CMC information for only those sections that have been changed and/or updated. Review of the resubmission is performed by the following product quality disciplines: drug product, process, and microbiology. The proposed changes in the resubmission are deemed acceptable and the NDA is recommended for Approval from the product quality perspective.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A.

D. Final Risk Assessment

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.

27-Dec-2017



Xiao
Chen

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Date: 1/02/2018 11:04:42AM

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MICROBIOLOGY[IQA Review Guide Reference](#)**Product Background:**

NDA: 207970

Drug Product Name / Strength: Cabazitaxel, 10 mg/ml (60mg/6ml, (b) (4))

Route of Administration: Intravenous infusion

Applicant Name: Actavis LLC

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary: NDA 207970 was previously reviewed and deemed adequate from the perspective of product quality microbiology on 6/17/2015 (N270970.doc). The 11/2/2017 resubmission contains a proposed increase to the post-dilution in-use storage time, the removal of a table in the bacterial endotoxins testing protocol, and the addition of a scaled-down batch size for the 60 mg/6 ml formulation of the drug product.

List Submissions Being Reviewed: 11/02/2017 and 03/06/2015

Highlight Key Outstanding Issues from Last Cycle: NA.

Remarks: eCTD submission.

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: Microbiology quality review N207970.docx dated 6/17/2015.

List Number of Comparability Protocols (ANDA only): None.

CHANGES PROPOSED IN THIS RESUBMISSION

NDA 207970 was previously reviewed and deemed adequate from the perspective of product quality microbiology on 6/17/2015 (N270970.doc). This 11/2/2017 resubmission contains a labeling change that proposes to extend the post-dilution in-use storage time from (b) (4) hours to 72 hours under refrigeration conditions. The applicant included the following two CMC changes in the cover letter that are not assessed in this review:

- 1) The addition of a scaled-down batch size to the 60 mg/6 ml formulation of the drug product. There is no change to the (b) (4) parameters, and the previously reviewed (b) (4) data support the new batch size (6/17/2015, N270970.doc).
- 2) It was stated in the 11/2/2017 resubmission that a change was implemented to the Bacterial Endotoxin method; however, the nature of this change was unclear from the documents provided. The following information request was sent to the applicant by the drug product reviewer on 11/9/2017.

In your November 2, 2017 amendment to NDA 207970 for requesting final approval, you provided revised CMC information for the following sections:

Methods:

(b) (4)
Bacterial Endotoxin, GTM-16-V5, provided in Module 3.2.P.5.2
(b) (4)

For the updated CMC information described above, indicate the changes using a side-by-side comparison of the relevant sections in the original NDA. Provide rationale and justification for those changes.

Applicant Response

The applicant clarified that a table was removed from the Bacterial Endotoxin Protocol “GTM-16-V4” and placed in a separate document for reference (CM-004). The new Bacterial endotoxins protocol has been renamed “GTM-16-V5” and does not contain any changes to the bacterial endotoxins methodology previously deemed adequate (6/17/2015, N270970.doc); therefore, the document was not assessed in this review.

INFORMATION TO SUPPORT THE PROPOSED CHANGES

In-Use Storage Time

(3/6/2016, 3.2.P.8.1, CM-004-15-R Microbial Stability Testing with Microorganisms Report and CM-004-15-R Microbial Stability Testing with Microorganisms Protocol)

The applicant submitted a microbial stability study report in support of the proposed in-use storage time extension from (b) (4) hours to 72 hours under refrigeration conditions (3/6/2016, CM-004-15-R Microbial Stability Testing with Microorganisms Report). The

(b) (4)



The acceptance criterion of $< \text{(b) (4)}$ log increase was met for all conditions and it was concluded that the drug product is stable at 2-8°C for 72 hours post-dilution.

Adequate

Reviewer's Assessment: The applicant has met regulatory expectations for demonstrating the microbiological stability of the diluted drug product for the proposed post-dilution in-use storage conditions of 72 hours at 2-8°C.

List of Deficiencies: None.

Primary Microbiology Reviewer Name and Date: Christine M. Craig, Ph.D., December 14, 2017.

Secondary Reviewer Name and Date (and Secondary Summary, as needed): John W. Metcalfe, Ph.D., December 14, 2017. I concur with the primary reviewer's assessment.



John
Metcalf

Digitally signed by John Metcalfe

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Comments: I concur with the primary reviewer's assessment.



Christine
Craig

Digitally signed by Christine Craig

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Xiao
Chen

Digitally signed by Xiao Chen

Date: 1/02/2018 12:30:27PM

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NDA 207970

Cabazitaxel Injection, 10 mg/mL
(^{(b) (4)} **60 mg/6 mL**)

Actavis LLC

Debasis Ghosh, M. Pharm., Ph.D.
Review Chemist

Office of New Drug Products (ONDP)
Division of New Drug API
Branch II

CMC REVIEW OF NDA 207970
For the Division of Drug Oncology Products 1

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 207970
2. REVIEW #: 1
3. REVIEW DATE: 7/28/2015
4. REVIEWER: Debasis Ghosh, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	SD001	10/23/2014	10/23/2014
Quality Response to Information Request	SD002	12/18/2014	12/18/2014
Labeling/PI Data	SD003	01/28/2015	01/28/2015
Quality Response to Information Request	SD007	03/16/2015	03/16/2015
Quality Response to Information Request	SD009	04/23/2015	04/23/2015
Quality Response to Information Request	SD0010	06/10/2015	06/10/2015

7. NAME & ADDRESS OF APPLICANT:

Name: Actavis LLC
 Address: 400 Interspace Parkway
 Morris Corporate Center III
 Building D
 Parsippany, NJ, USA
 Representative: Joanne Stavole, Director, Regulatory Affairs
 Telephone: 862-262-7735

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
- b) Non-Proprietary Name: Cabazitaxel Injection
- c) Code Name/# (ONDQA only): NA
- d) Chem. Type/Submission Priority (ONDQA only):

CMC Review Data Sheet

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Microtubule stabilizer and antineoplastic

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 10 mg/mL (^{(b) (4)} 60 mg/6 mL)

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE¹	STATUS²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	4/2/2015	LOA (dated 6/23/14) provided. The DMF is active as of the date of this review.
	III		3	Adequate	NA	LOA (dated 6/5/14) provided. The DMF is active as of the date of this review. Last review was completed in Oct 2014.	
	III		3	Adequate	NA	LOA (dated 9/2/14) provided. The DMF is active as of the date of this review. Last review was completed in 2004.	
	III		3	Adequate	NA	LOA (dated 5/29/14) provided. The DMF is active as of the date of this review. The last review was done in Feb 2015.	
	V		1	Adequate	4/5/2015	LOA (dated 5/29/14) provided. Reviewed by the Division of Microbiology.	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	201023	Listed drug JEVTANA® was approved under NDA 201023.

18. STATUS:

ONDP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
OPF	'overall acceptable" (see page 61 of this review)	7/21/15	Robert Wittorf
Pharm/Tox			Kimberly Ringgold
Biopharm			Elsbeth Chikhale
LNC			
Methods Validation	NA		
DMEPA*	Recommended some minor revisions (see DARRTS)	06/19/2015	Davis Mathew and Chi-Ming Tu
EA	Categorical exclusion (see review)	Same as this review date	Debasis Ghosh
Microbiology	"Recommended for approval"	06/24/2015	Denise Miller and Neal Sweeney

*DMEPA: Division of Medication Error Prevention and Analysis; OPF: Office of Process and Facility; EA: Environmental Assessment

Executive Summary Section

The CMC Review for NDA 207970

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. An “overall acceptable” site recommendation from the Office of Process and Facility has been made. Therefore, from a CMC perspective, this NDA is recommended for approval pending the satisfactory resolution of labeling issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

(b) (4)



Executive Summary Section

(b) (4)

(2) Drug Product

The drug product, Cabazitaxel Injection (10 mg/mL), is a sterile, clear, oily, light yellow (b) (4) solution in a single-dose vial. It is formulated as a solution concentrate intended for intravenous infusion after dilution with appropriate infusion solution (0.9% Sodium Chloride or 5% Dextrose). It is packaged in a (b) (4) clear glass vial (b) (4) with rubber stoppers with (b) (4) seals. The configuration for each vial is (b) (4) 60 mg/6 mL.

The listed drug is Jevtana® (cabazitaxel) Injection, 60 mg/1.5 mL, co-packaged with a diluent vial containing 5.7 mL of a 13% w/w aqueous solution of alcohol (b) (4). The diluent is to be used for the preparation of a premix solution of 10 mg/mL of cabazitaxel, followed by a second dilution of the appropriate dose in 0.9% sodium chloride solution or 5% dextrose solution in an infusion bag.

The proposed product eliminates the need for two-vial formulation and the preparation of pre-mix solution. Both proposed Cabazitaxel Injection, 10 mg/mL and the pre-mix solution of Jevtana® contain cabazitaxel ((b) (4) or acetone solvate for Jevtana), alcohol, and polysorbate 80. In addition to the above active and inactive ingredients, the proposed Cabazitaxel Injection contains polyethylene glycol 400 and anhydrous citric acid. The applicant claimed that

Executive Summary Section

(b) (4)

(b) (4) It has been noted that pre-mix of Jevtana® contains water as part of the diluent. The diluted infusion solutions of both formulations (proposed and Jevtana®) appear to be equivalent in terms of its physico-chemical behavior. (b) (4)

The applicant performed several studies to demonstrate the fact that the inclusion of citric acid and PEG400 in this new formulation did not significantly affect (b) (4) stability (b) (4).

The drug product was manufactured at Sindan Pharma, Romania. The site has received 'overall acceptable' recommendation from the Office of Process and Facility on July 21, 2015. The method of manufacturing involves (b) (4). The applicant provided flow sheet of the process and Master Batch Records for three commercial batches from (b) (4) 60 mg/6 mL (b) (4). Based on Microbiology review (DARRTS 6/24/15), the manufacturing process & process controls, process validation and container closure integrity are adequate to support the proposed sterile product.

The drug product specification includes critical quality attributes of drug product, test methods and acceptance criteria. All non-compendial test methods were validated for the intended use. The impurities listed (b) (4) are derived from (b) (4). The applicant provided batch analysis data for exhibit batches: 3 (b) (4) 60 mg/6 mL. The batches were manufactured using four different drug substance batches. All batched met the proposed specification.

Cabazitaxel Injection, 10 mg/ mL ((b) (4) 60 mg/6 mL) will be provided in a (b) (4) glass vial, (b) (4). The applicant provided letter of authorizations (LOAs) for the referenced DMFs for the components of the container closure system. The DMFs were found to be adequate to support this NDA.

Based on photo stability study, the product appears to be stable in the proposed container closure system. Stability study with the diluted infusion solution showed physicochemical stability of the solution for (b) (4) hours at ambient temperature and 72 hours at refrigerated conditions. However, during a recent communication, the microbiology reviewer noted that the post reconstitution study that they submitted supports only 8 hours at room temperature and (b) (4) hours at refrigerated conditions. Hence, we recommend that the diluted infusion solution must be used within 8 hours at ambient temperature and (b) (4) hours at refrigerated conditions.

Based on the stability study performed at long-term (25°C/60%RH), and intermediate (30°C/65%RH) conditions for 12 months and accelerated (40°C/75%RH) conditions for 6 months with both normal and inverted vial positions, the recommended shelf-life is 24 months with following storage conditions: (b) (4)

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

Cabazitaxel is a microtubule inhibitor. It is indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen. Cabazitaxel Injection (10 mg/mL) single-dose vial ((b) (4) 60 mg/6 mL) should be diluted with infusion solution (0.9% sodium chloride solution or 5% dextrose solution) prior to use. The concentration of the cabazitaxel injection final infusion solution should be between 0.10 mg/mL and 0.26 mg/mL. If the cabazitaxel injection final infusion solution is not clear or appears to have precipitated, it should be discarded. Cabazitaxel injection should not be mixed with any other drugs. Cabazitaxel injection (b) (4) mg/m² administered every three weeks as a one-hour intravenous infusion at room temperature in combination with oral prednisone 10 mg administered daily throughout cabazitaxel injection treatment.

C. Basis for Approvability or Not-Approval Recommendation (to be completed)

This NDA is recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint. See also Risk Assessment in Appendix I.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Debasis Ghosh, M. Pharm., Ph.D.,
Quality Assessment Lead
Branch II
Division of New Drug API
Office of New Drug Product

Debasis
Ghosh -A

Digitally signed by Debasis Ghosh -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Debasis Ghosh -
A,
0.9.2342.19200300.100.1.1=2000571655
Date: 2015.07.28 14:19:29 -04'00'

B. Endorsement Block:

(See appended electronic signature page)

Olen Stephens, Ph.D.,
Acting Branch Chief
Branch II (Oncology)
Division of New Drug Products I
Office of New Drug Product

Olen
Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2015.07.28 15:27:00 -04'00'

C. CC Block: entered electronically in DARRTS

CMC Assessment Section

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

[See also DMEPA comments in DARRTS]

The following is a summary of the labeling review.

1. Package Insert

(a) “Highlights” Section

Item	Reviewer’s Comment
Drug name (201.57(a)(2))	
Proprietary name and established name	Adequate; No proprietary name
Dosage form, route of administration	Adequate
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (201.57(a)(8))	
Whether the drug product is scored	NA

Following changes are recommended in the PI:

- Replace [redacted] (b) (4)

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths

Item	Reviewer’s Comment
Available dosage forms	Yes
Strengths: in metric system	Yes
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

Following changes are recommended in the PI:

- Replace [redacted] (b) (4)

CMC Assessment Section

#11: Description

Item	Reviewer's Comment (also see below)
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Yes
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Yes
Statement of being sterile (if applicable) (201.57(c)(12)(D))	Yes
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Yes

Following changes are recommended in the PI:

1) Replace  (b) (4)
 (b) (4)

Replace the structure of cabazitaxel with

 (b) (4)

2) Replace  (b) (4)
 (b) (4)

CMC Assessment Section

3) Replace [redacted] (b) (4)

[redacted] (b) (4)

4) Replace [redacted] (b) (4) with “polyethylene glycol 400”

5) Replace [redacted] (b) (4)

[redacted] (b) (4)

#16: How Supplied/Storage and Handling

Item	Reviewer’s Comment
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Following changes are recommended in the PI:

1) Replace “Cabazitaxel injection” with “Cabazitaxel Injection”.

2) Replace [redacted] (b) (4) with “single-dose”.

3) Replace [redacted] (b) (4)

4) Replace [redacted] (b) (4)

5) Replace [redacted] (b) (4)

[redacted] (b) (4)

6) Replace “15° to 30°C” with “15°C to 30°C” (may have been already communicated by DMEPA, see DMEPA review in DARRTS).

2. Immediate container labels

A copy of the container label is provided below:

CMC Assessment Section



(b) (4)

Item	Reviewer's Comment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Appears to be acceptable
Dosage strength	Yes, consistent with USP<1>
Net contents (See USP <1> for presentation of strength and content for injections.)	Yes, consistent with USP<1>
"Rx only" displayed prominently on the main panel	Yes
NDC number (21 CFR 207.35(b)(3)(i)) (Appear prominently in the top third of the principal display panel or it may appear as part of and contiguous to any bar-code symbol)	Yes
Lot number and expiration date (21 CFR 201.17)	Yes
Storage conditions	Yes
Bar code (21CFR 201.25)	Yes
Name of manufacturer/distributor	Yes
Instruction for Medication Guide, if any (21CFR 208.24(d)) appears prominently	Yes
And others, if space is available	Prominent Display (b) (4)

Evaluation: Adequate

See DMEPA review for the suggested changes. No additional comments from CMC.

CMC Assessment Section

4. Carton labeling

A copy of the carton label is provided below:



Item	Reviewer's Comment
Proprietary name, established name (font size, prominence)	Appears to be acceptable
Dosage strength	Consistent with USP<1>
Net quantity of dosage form	Consistent with USP<1>
"Rx only" displayed prominently on the main panel	Yes

CMC Assessment Section

Lot number and expiration date	Yes
Storage conditions	Yes
Bar code (21CFR 201.25)	Yes
NDC number (21 CFR 207.35(b)(3)(i))(Appear prominently in the top third of the principal display panel or it may appear as part of and contiguous to any bar-code symbol)	Yes
Manufacturer/distributor's name	Yes
Quantitative ingredient information (injectables)	Yes
Statement of being sterile (if applicable)	Yes
"See package insert for dosage information"	Yes
Special instructions ("Keep out of reach of children" is required for OTC in CFR. Optional for Rx drugs)	Yes

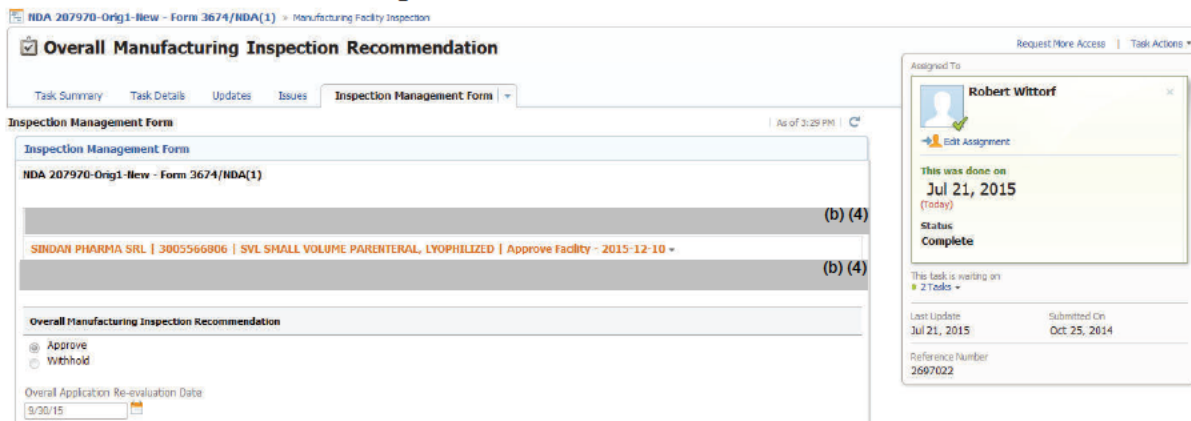
Evaluation: Adequate

See DMEPA review for the suggested changes. No additional comments from CMC.

B. Environmental Assessment Or Claim Of Categorical Exclusion

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31(b). The basis of this exclusion is the fact that the estimated concentration of the active ingredient at the point of entry into the aquatic environment will be less than 1 ppb from all products using this material as the active ingredient.

C. Establishment Evaluation Report



III. List Of Deficiencies Communicated and Resolved

- Harmonize release and stability specifications (assay of cabazitaxel and total impurities) for drug product.

CMC Assessment Section

Appendix I:

Risk Assessment : Cabazitaxel Injection, 10 mg/mL (b) (4) 60 mg/6 mL)

Product Property/ Impact of changes/ CQAs	Changes and Variations	Failure Mode	Initial Risk Ranking	Mitigation Noted in Review	Final Risk Ranking	Considerations for Lifecycle
Sterility	Formulation Container Closure Process Parameters Scale/ Equipments Site	(b) (4)	High	(b) (4)	Low	(b) (4)
Endotoxin (pyrogen)	Formulation Container Closure Process Parameters Scale/Equipments Site		High		Low	
Assay (API), Stability	Formulation Container Closure Raw Materials Process parameters Scale/Equipments Site		High		Low	
Physical Stability (solid state)	NA		NA		NA	
Assay (preservative)	NA		NA		NA	
Assay (antioxidant)	NA		NA		NA	
Uniformity of dose (fill)	Formulation		Low		Low	

CMC Assessment Section

Product Property/ Impact of changes/ CQAs	Changes and Variations	Failure Mode	Initial Risk Ranking	Mitigation Noted in Review	Final Risk Ranking	Considerations for Lifecycle
volume/deliverable volume)	Container Closure Process Parameters Scale/Equipments Site	(b) (4)		(b) (4)		(b) (4)
Content Uniformity (suspension)	NA		NA		NA	
Osmolality	Formulation Container Closure Raw Materials Process Parameters Scale/Equipments Site		Medium		Low	
pH (low)	Formulation Container Closure Process Parameters Scale/Equipments Site		Low		Low	
pH (High)	NA		NA		NA	
Particle Size distribution (suspension)	NA		NA		NA	
Particulate matter (non- aggregate for solution only)	Formulation Container Closure Raw Materials Process Parameters Scale/Equipments Site		High		Low	

CMC Assessment Section

Product Property/ Impact of changes/ CQAs	Changes and Variations	Failure Mode	Initial Risk Ranking	Mitigation Noted in Review	Final Risk Ranking	Considerations for Lifecycle
		(b) (4)		(b) (4)		(b) (4)
Leachable/Extractable	Formulation Container Closure Raw Materials Process Parameters Scale/Equipments Site		Low		Low	
Appearance (color/turbidity)	Formulation Container Closure Raw Materials Process Parameters Scale/Equipments Site		Low		Low	

NA = Not applicable; API= Active Pharmaceutical Ingredient; CQA = Critical Quality Attribute; RLD = Registered Listed Drug

Product Quality Microbiology Review

17 June 2015

NDA: 207-970/N000

Drug Product Name

Proprietary: NA

Non-proprietary: Cabazitaxel Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
23 October 2014	23 October 2014	30 October 2014	31 October 2014
10 March 2015	10 March 2015	NA	NA

Submission History (for 2nd Reviews or higher) – NA

Applicant/Sponsor

Name: Actavis LLC

Address: 400 Interpace Parkway
Morris Corporate Center III, Building
Parsippany NJ 07054

Representative: Joann Stabile, M.S., R.A.C
Director, Regulatory Affairs

Telephone: (980) 659-2250

Name of Reviewer: Denise A. Miller

Conclusion: Recommended for approval from a quality microbiology perspective.

Product Quality Microbiology Data Sheet

- A. 1. TYPE OF SUBMISSION:** Original New Drug Application
- 2. SUBMISSION PROVIDES FOR:** The manufacture and marketing of the subject drug product.
- 3. MANUFACTURING SITE:**
S.C. Sindan-Pharma S.R.L.
11th Ion Mihalache Boulevard
Bucharest 1 Romania
FEI Number 3005566806
- 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Dosage Form: Sterile Solution in single use vials containing (b) (4) 6 mL
 - Route of Administration: Intravenous
 - Strength/Potency: 10 mg/mL ((b) (4) 60 mg/6 mL)
- 5. METHOD(S) OF STERILIZATION:** (b) (4)
- 6. PHARMACOLOGICAL CATEGORY:** treatment of hormone-refractory metastatic prostate cancer in combination with prednisone in patients previously treated with a docetaxel-containing treatment regime.

B. SUPPORTING/RELATED DOCUMENTS:

DMF (b) (4): Type V DMF (b) (4). The Letter of Authorization was dated for May 29, 2014 (b) (4) and the 13 December 2013 amendment. This amendment was reviewed by Division of Microbiology on 05 April 2015 and was adequate.

filename: N207970.docx

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended for approval from a quality microbiology perspective.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** - NA

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This is a single use non-aqueous product that (b) (4) is diluted prior to infusion.
- B. Brief Description of Microbiology Deficiencies** – There were no deficiencies identified in the information provided.
- C. Contains Potential Precedent Decision(s)-** Yes No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O ^(3, 4, 5)	Severity of Effect (S)	Detect. (D)	Risk Priority Number ⁶ (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	10	-1 ⁽³⁾ +1 ⁽⁴⁾	5	5	250	Simulations and interventions conducted (b) (4) Environmental monitoring
Endo		4		4	4	64	

(b) (4)

3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) (b) (4)

4 = Post-Constitution/-Dilution Hold Times in Labeling, modifies O (+1) [emphasize Labeling instructions for administration, dosing, storage conditions, and specified diluents. Microbial challenge studies supporting label recon/dilution/storage instructions if >4 hr RT or >24 hr refrig.]

5 = Components derived from animal sources, modifies O (+1) [emphasize Component bioburden, TSE/BSE-free documentation (TS and AP), viral inactivation studies (AP), bioburden reduction processes.]

6 = RPN = O(after modification when applicable)×S×D
 RPN <50 = **Low Risk**; RPN 50-120 = **Moderate Risk**; RPN >120 = **High Risk**

B. Final Risk Assessment -

Sterility: This is a high risk product (b) (4)

(b) (4). The risk of a non-sterile product is minimized by the non-aqueous formulation of the drug product, the validation of the sterilization process (b) (4)

(b) (4) validation studies, and microbial studies to support the post dilution hold times recommended in the labeling.

Endotoxin: The risk for endotoxin is minimized by the validation of the (b) (4) container closure components to reduce endotoxin (b) (4). The final filled product is tested for endotoxin and the proposed specification is within the USP <85> recommendations for a drug administered by surface area.

IV. Administrative

A. Reviewer's Signature _____

Denise A. Miller

Microbiologist, OPF/DMA/Branch II

B. Endorsement Block _____

Neal J. Sweeney, Ph.D.

Senior Microbiologist, OPF/DMA/Branch II

C. CC Block

N/A

Product Quality Microbiology Assessment

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA**

S DRUG SUBSTANCE - NA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product is a non-aqueous concentrate intended for intravenous infusion after dilution with either 0.9% Sodium Chloride or 5% Dextrose solution. The product is sterile, clear, oily, light yellow solution in a single use vial.
- Drug product composition – The composition was provided in section 2.3.P.1 of the application. The components included cabazitaxel, anhydrous citric acid, (b) (4) alcohol, polysorbate 80 and polyethylene glycol 400. This is a non-aqueous product.
- Description of container closure system –
 - Vials: (b) (4)
 - Stoppers: (b) (4)



(b) (4)

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

/s/

DENISE A MILLER
06/24/2015

NEAL J SWEENEY
06/24/2015
I concur.