

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211225Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211225

Review 1

Drug Name/Dosage Form	Zykadia [®] (ceritinib (LDK378)) Film-Coated Tablet
Strength	150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceuticals Corporation
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000	05/18/2018	Original
0002	08/0/2018	Quality Responses to DP
0003	08/31/2018	Quality Responses to DP
0004	09/21/2018	Quality Responses to DP and Process/Facility
0005	11/15/2018	Quality Responses to Process/Facility
0007	12/07/2018	Quality Responses to DP, Labeling, and Biopharm
0008	01/07/2019	Quality Responses to DP, Labeling, and Biopharm

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gaetan Ladouceur	Suong Tran
Drug Product	Amit Mitra	Anamitro Banerjee
Process	Quamrul Majumder	Bogdan Kurtyka
Microbiology	Quamrul Majumder	Bogdan Kurtyka
Facility	Quamrul Majumder	Bogdan Kurtyka
Biopharmaceutics	Zhuojun Zhao	Banu Zolnik
Regulatory Business Process Manager	Priyanka Kumar/Steven Kinsley	NA
Application Technical Lead	Nina Ni	NA
Laboratory (OTR)	NA	NA



QUALITY ASSESSMENT



ORA Lead	Caryn McNab	NA
Environmental	Amit Mitra	Anamitro Banerjee

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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	Not Applicable (NA)	Adequate information for the container/closure system is provided in the NDA
	Type III		Adequate	NA	Adequate information for the container/closure system is provided in the NDA	
	Type III		Adequate	NA	Adequate information for the container/closure system is provided in the NDA	
	Type III		Adequate	NA	Adequate information for the container/closure system is provided in the NDA	
	Type III		Adequate	NA	Adequate information for the container/closure system is provided in the NDA	
	Type III		Adequate	NA	Adequate information for the container/closure system is provided in the NDA	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205755	Ceritinib capsule was approved under NDA 205755. The entire Modules 4 and 5 as well as Module 3 DS of this NDA are referenced to NDA 205755.

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

From the chemistry, manufacturing, and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

II. Summary of Quality Assessments

A. Product Overview

Ceritinib (capsules), tradename ZYKADIA[®], received accelerated approval under NDA 205755 on April 29, 2014 for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. On May 26, 2017, ZYKADIA[®] was approved for the new/expanded indication for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test (NDA 205755/S-009). New recommended daily dose of 450 mg with food was approved on December 21, 2017 (NDA 205755/S-010). Ceritinib was granted Orphan Designation on September 27, 2013 for the treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive.

In accordance with 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, on May 18, 2018, Novartis Pharmaceuticals Corporation submitted NDA 211225 for a new dosage form for ZYKADIA[®] (ceritinib), 150 mg film-coated tablet (FCT) as a bioequivalent, interchangeable, replacement for ZYKADIA[®] (ceritinib), 150 mg capsule. The smaller tablet size compared to the hard gelatin capsule is expected to be easier for patient to swallow and resulting in better patient adherence to ceritinib treatment. Ceritinib film-coated tablet was developed at three dosage strengths (150 mg, 300 mg, and 375 mg) which were used in clinical evaluation and shown to be bioequivalent to the 150 mg hard gelatin capsule. In this submission, only the 150 mg film-coated tablet is proposed to be commercialized. The recommended dose is 450 mg taken orally once daily with food.

After approval of the film-coated tablet, the applicant does not plan to maintain both dosage forms on the US market. Once the capsule inventory is depleted from the US market (estimated by end of 2019), Zykadia[®] will only be available as the film-coated tablet in the US. The Zykadia[®] capsule NDA 205755 will remain active since the tablet NDA 211225 makes cross-reference to it.

Proposed Indication(s) including Intended Patient Population	For the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test
Duration of Treatment	Continue treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	450 mg orally once daily with food
Alternative Methods of Administration	NA

B. Quality Assessment Overview

1. Drug Substance [Ceritinib]

The drug substance ceritinib has the following chemical name, structural formula, molecular formula, and molecular weight:

International Non-proprietary Name (INN): Ceritinib

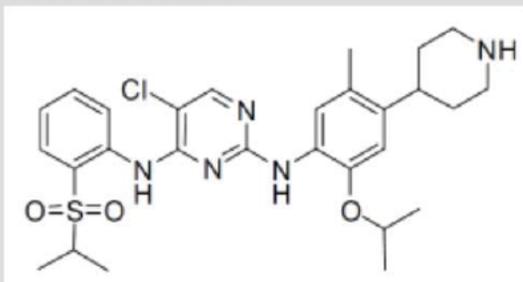
Chemical Name: 5-Chloro-2-N-{5-methyl-4-(piperidin-4-yl)- 2-[(propan-2-yl) oxy]phenyl}-4-N-[2-(propane-2-sulfonyl) phenyl] pyrimidine2,4-diamine

(CAS) Registry Number: 1032900-25-6

Mol. Formula: C₂₈H₃₈N₅O₃ClS

Mol. Wt.: 558.1 g/mole

Structural Formula:



Ceritinib is a white to almost white or light yellow powder. Ceritinib is reported to be non-hygroscopic and does not show isomerism. (b) (4)

Ceritinib is considered as a BCS Class 4 (low solubility, low permeability) drug. Its solubility in 0.1N HCl is 11.9 mg/mL; however, the solubility decreases substantially with increasing pH. Its water solubility is (b) (4).

Complete CMC information for ceritinib drug substance is maintained in the approved NDA 205755 and cross-referenced to this NDA. There is no new CMC information provided for ceritinib drug substance in this NDA.

Facilities:

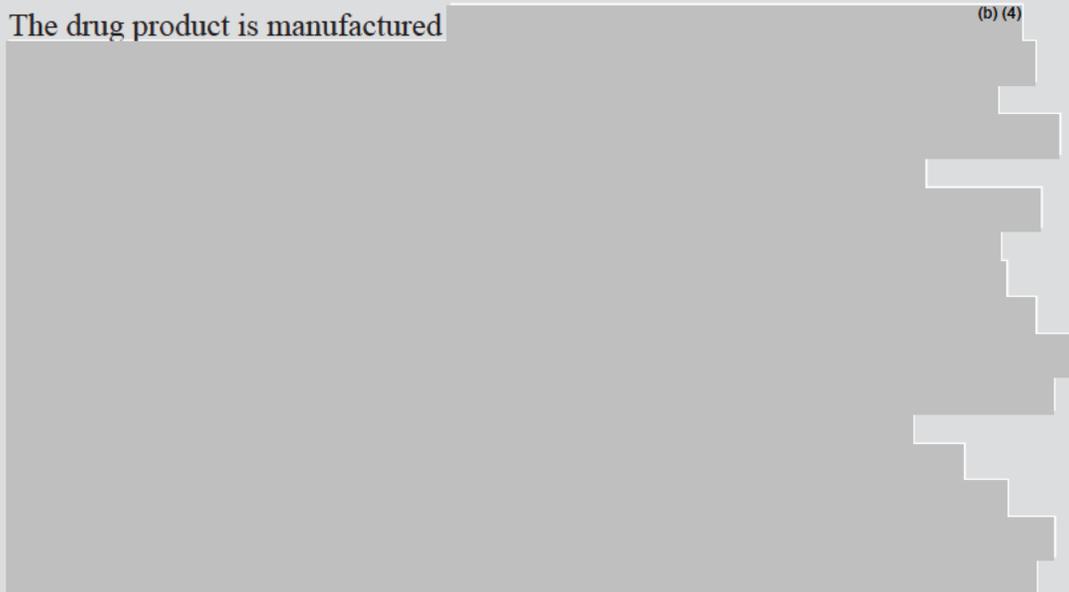
Office of Process and Facilities (OPF/OPQ/CDER) has recommended “Acceptable” for the following drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on inspection history and manufacturing capacity:



2. Drug Product [(b) (4) tablets]

The proposed commercial drug product, ceritinib film-coated tablets, 150 mg are light blue, round, biconvex film-coated with beveled edges, no score, debossed with “NVR” on one side and “ZY1” on the other side and are packaged in 90 cc high density polyethylene (HDPE) bottles (b) (4) for trade pack (with (b) (4) counts) and in 45 cc HDPE bottles for sample pack (with 21 counts). The capsule dosage form at 150 mg strength is a marketed drug product under the same trademark “Zykadia”.

The drug product is manufactured



Drug product is release tested for: Appearance by visual inspection, mean mass by weight, identification by HPLC and UV, assay by HPLC, degradation products by HPLC, dissolution by UV, content uniformity by mass variation, and water content by Karl Fischer. The forced degradation study has established that the HPLC

method for assay and degradation products is stability indicating. The HPLC validation results for identification, assay, and degradation product is found adequate.

(b) (4)

The applicant conducted 12 months long term (25°C/65% RH) and 6 months accelerated (40°C/75%RH) stability for 3 registration stability batches of 150 mg ceritinib tablets in HDPE bottles. All results show that there are no trends and no significant changes observed on assay, degradation products, dissolution rate, water content, and microbial enumeration test and support the proposed acceptance criterion of each test. Based on the available stability data provided in this NDA, a tentative expiration date of 24 months may be granted (as proposed by the applicant) when the drug product is stored 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]”. The submitted photo-stability study results on the primary batches indicate that the drug product does not require protection from light.

Biopharmaceutics:

The applicant has adequately demonstrated the suitability of the dissolution method [with an acceptance criterion of NLT $\frac{(b)}{(4)}\%$ (Q value in 15 minutes)] for batch release and stability testing. The dissolution method, i.e. 900 mL 0.01 HCl (pH 2) using USP I (Basket) at 75 RPM is adequately justified. The proposed dissolution method is acceptable for the QC dissolution testing of the proposed drug product. The discriminating power of the proposed dissolution method with regards to process parameters and DS particle size is limited, (b) (4)

. The applicant also provided adequate dissolution data to support the bridging between the biobatch and the proposed commercial drug product (with reduced coating weight).

Facilities:

Office of Process and Facilities (OPF/OPQ/CDER) has recommended “Acceptable” for the following drug product manufacturers (for manufacture, release testing, stability testing, packaging, and labeling) based on inspection history and manufacturing capacity:

(b) (4)

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see below)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, Stability (API)	<ul style="list-style-type: none"> • Formulation • Container/closure • Process parameter • Scale/equipment • Site 	L	(b) (4)	L	Continue stability monitoring post approval
Physical Stability (solid state)	<ul style="list-style-type: none"> • Formulation • Container/closure • Process parameter • Scale/equipment • Site 	L		L	None

			(b) (4)		
Uniformity of dose	<ul style="list-style-type: none"> • Formulation • Container/closure • Process parameter • Scale/equipment • Site 	L		L	None
Microbial limits	<ul style="list-style-type: none"> • Formulation • Container/closure • Process parameter • Scale/equipment • Site 	L		L	Not being monitored as recommended in ICH Q6A
Dissolution	<ul style="list-style-type: none"> • Formulation • Container/closure • Process parameter • Scale/equipment • Site 	M		L	None
Moisture content	<ul style="list-style-type: none"> • Formulation • Container/closure • Process parameter • Scale/equipment • Site 	L		L	None

			(b) (4)		
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LABELING

R Regional Information (NDA 211-225)

1.14 Labeling

1. Package Insert: Is being conducted with the labeling review. ***

(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Zykadia Established Name: (ceritinib) tablets	Satisfactory
Dosage form, route of administration	tablets, oral	Satisfactory
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: 150 mg	Satisfactory

Reviewer’s Assessment: The highlight is satisfactory with respect to proprietary and established name, dosage form and strengths. The PI is yet to be finalized.

(b) "Full Prescribing Information" Section
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

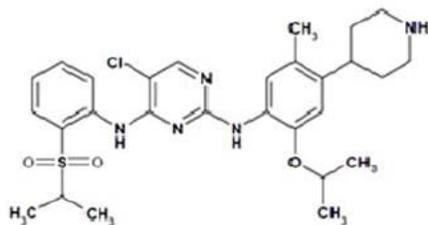
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Satisfactory
Strengths: in metric system	150 mg	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	150 mg tablet, light blue, round, bi-convex with beveled edges, without score, debossed with "NVR" on one side and "ZY1" on the other side.	Satisfactory

Reviewer's Assessment: This section may be modified according to PLR, if needed.

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

ZYKADIA (ceritinib) is a tyrosine kinase inhibitor for oral administration. The molecular formula for ceritinib is $C_{28}H_{36}N_5O_3ClS$. The molecular weight is 558.14 g/mol. Ceritinib is described chemically as 5-Chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine.

The chemical structure of ceritinib is shown below:



Ceritinib is a white to almost white or light yellow powder

(b) (4)

ZYKADIA is supplied as printed hard-gelatin capsules containing 150 mg of ceritinib and the following inactive ingredients: colloidal silicon dioxide, low substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and hard gelatin capsule shells. The capsule shell is composed of FD&C Blue # 2, gelatin, and titanium dioxide.

ZYKADIA is also supplied as film-coated tablets, containing 150 mg of ceritinib and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose and povidone. The tablet coating contains FD&C Blue # 2 aluminum lake, hypromellose, polyethylene glycol, talc and titanium dioxide.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: ZYKADIA Established name: ceritinib tablets	Satisfactory
Dosage form and route of administration	Tablets, Oral	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	Salt is not used	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Satisfactory	Satisfactory for oral dosage form
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Tyrosine kinase inhibitor	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	(b) (4)	Satisfactory

Reviewer’s Assessment: The “Description Section” is satisfactory.

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

ZYKADIA film-coated tablets			
Package Configuration	Capsule/Tablet Strength (mg)	NDC	Print(description)
84 count bottle	Tablet/150 mg	0078-XXXX84	Film-coated tablet, light blue, round, biconvex with beveled edges, without score, debossed with “NVR” on one side and “ZY1” on the other side.

Handling and Disposal:

Storage: (b) (4)

The applicant was requested to revise the statement 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] to comply with the current USP standard storage language. In an amendment, the applicant complied with the FDA’s request. The final label is yet to be finalized.

Reviewer’s Assessment: No special handling of this drug product is needed based on the first labeling meeting.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	150 mg tablets	Satisfactory
Available units (e.g., bottles of 100 tablets)	84 counts	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Film-coated tablet, light blue, round, biconvex with beveled edges, without score, debossed with "NVR" on one side and "ZY1" on the other side.	Satisfactory
Special handling (e.g., protect from light, do not freeze)	None	Satisfactory
Storage conditions	Change ^{(b) (4)} [redacted] 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]."	Satisfactory

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: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936	Satisfactory

Immediate Container Label

150 mg tablets

(b) (4)

Reviewer's Assessment:

The applicant provided the following required items: Established name, dose strength, prescription only, lot #, bar code, and expiration date. DMEPA may have additional comments. Based on an IR, the applicant agreed to change the storage conditions to comply with the current storage recommendation (b) (4) 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] on the immediate container label and the PI. The applicant revised the container label (see below). The revised container label is satisfactory to the reviewer.

Revised container label

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Zykadia Established name: ceritinib tablets	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Correct strength was included (150 mg)	Satisfactory
Net contents (21 CFR 201.51(a))	84 tablets	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Included	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*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.

**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.

Reviewer's Assessment: Satisfactory

Carton Labeling: Not submitted for trade package.

Reviewer's Assessment: The labels are satisfactory.

List of Deficiencies: None

Primary Labeling Reviewer Name and Date:

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



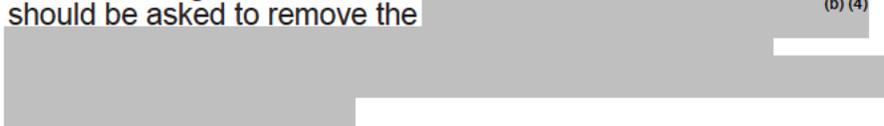
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Comments: Agree with Dr. Mitra's assessment. The applicant
should be asked to remove the ^{(b) (4)}



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BIOPHARMACEUTICS

Application No: NDA 211225-ORIG-1 [505(b)(1)]

Drug Product Name / Strength: ZYKADIA[®] (Ceritinib) tablets, 150 mg

Route of Administration: Oral

Applicant Name: Novartis Pharmaceuticals Corporation

Biopharmaceutics Review Team:

Primary Reviewer: Zhuojun Zhao, PhD

Secondary Reviewer: Banu Zolnik, PhD

Product Background:

Ceritinib is a potent inhibitor of anaplastic lymphoma kinase (ALK) use in the treatment of patients with metastatic non -smal cell lung cancer (NSCLC). Novartis Pharmaceuticals Corporation submitted this NDA for a new dosage form, ZYKADIA[®] (ceritinib), 150 mg film-coated tablet (FCT), as a bioequivalent, interchangeable, replacement for ZYKADIA[®] (ceritinib) 150 mg capsule (NDA 205755).

Review Summary:

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting the proposed dissolution method and acceptance criterion, as well as formulation bridging in the drug product development.

In Vitro Dissolution Method and Acceptance Criterion:

Based on the provided dissolution data, the following dissolution methods and the revised acceptance criterion are acceptable and agreed upon:

Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP I (Basket)	75 RPM	0.01 N HCl (pH 2)	900 mL	NLT $\frac{(b)}{(4)}$ % (Q) at 15 minutes

Formulation Bridging:

The Applicant provided adequate dissolution data to support the bridging between the biobatch and the proposed commercial drug product (reduced coating weight).

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 211225 for ZYKADIA[®] (ceritinib) Tablets, 150 mg, is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

List of Submissions being reviewed:

Submissions Reviewed	Document Date
Original Submission	5/18/2018
IR Response	12/7/2018

I. Drug Substance

Ceritinib is a free form drug substance.

(b) (4)

Ceritinib is non-hygroscopic and does not show isomerism.

II. BCS Designation

The Applicant notes that the drug substance, Ceritinib, behaves like a BCS Class 4 compound with low solubility and low permeability.

Drug Substance Solubility:

The Applicant provided the solubility of Ceritinib over the physiologic pH range in Table 1.

Table 1. Solubility of Ceritinib drug substance

Solvent	Solubility (mg/mL) at 25°C
Water	0.02
0.1N HCl	11.9
0.01N HCl	5.5
0.001N HCl	0.64
pH 4.5	0.03
pH 5.0	0.04
pH 6.0	0.01
pH 6.8	0.01
pH 8.0	0.003
pH 9.0	0.1

Permeability:

In NDA 205755, the Applicant performed permeability experiments to compare Ceritinib to mannitol (a low permeability marker) and propranolol (high permeability marker) and classified the API as a low permeability drug¹.

III. Formulation:

Table 2 summarizes the qualitative and quantitative composition of the proposed immediate-release oral Ceritinib Tablets, 150 mg.

¹ DARRTS: NDA 205755 REV-QUALBIOPHARM-21 (Primary Review), final date 3/25/2014

Table 2. Composition of the Proposed Certinib Tablets, 150 mg

Ingredients	Amount per 150 mg film-coated tablet (mg)	Function	Reference to standards
(b) (4)			
Certinib ¹ (b) (4)	150.00	Active ingredient	Novartis monograph Ph. Eur., USP/NF
Microcrystalline cellulose (b) (4)			Ph. Eur., USP/NF
[redacted] hydroxypropyl cellulose (b) (4)			Ph. Eur., USP/NF
Povidone (b) (4)			Ph. Eur., USP/NF
Croscarmellose sodium			Ph. Eur., USP/NF
Magnesium stearate ² (b) (4)			Ph. Eur., USP/NF
Colloidal silicon dioxide (b) (4)			Ph. Eur., USP/NF
(b) (4)			
Total weight of film-coated tablet:	258.80		(b) (4)
(b) (4)			

IV. Dissolution Method:

The proposed dissolution method is summarized as follows:

USP Apparatus type	USP I (Basket)
Rotation (rpm)	75 RPM
Medium	0.01 N HCl (pH 2)
Volume (mL)	900 mL
Temperature	37±0.5 °C

The dissolution method was built based on the Applicant's experience gained with ZYKADIA® (Ceritinib) Capsules in NDA 205755². An overview of the development of the dissolution method for Ceritinib tablets is attached in [Appendix I](#). The Applicant provided the justification for the choice of dissolution apparatus, dissolution medium, and agitation speed in the [Pharmaceutical Development Report](#) and [Appendix 2 \(Dissolution: Method development and Discriminatory Capability\)](#) in module 3.2.P.2, as detailed below:

Medium Volume:

The Applicant selected a medium volume of 900 mL based upon sink conditions³ (Table 4) as well as its acceptance as a standard volume for the basket (b) (4).



Dissolution Medium pH:

Dissolution profiles of one clinical batch (X165LM) in dissolution media at different pH values are displayed in Figure 1. The Applicant selected 0.01N HCl (pH 2) as the dissolution medium due to the complete drug release observed relative to higher pH buffers.

² The approved dissolution method for ZYKADIA® (Ceritinib) Capsules in NDA 205755 is using USP II (Paddle) with 900 mL 0.01 M HCl at 60 rpm.

³ Based on the highest strength of the clinical Ceritinib tablet, 375 mg

Figure 1. Dissolution profiles for Ceritinib 150 mg film-coated tablet batch X165LM at



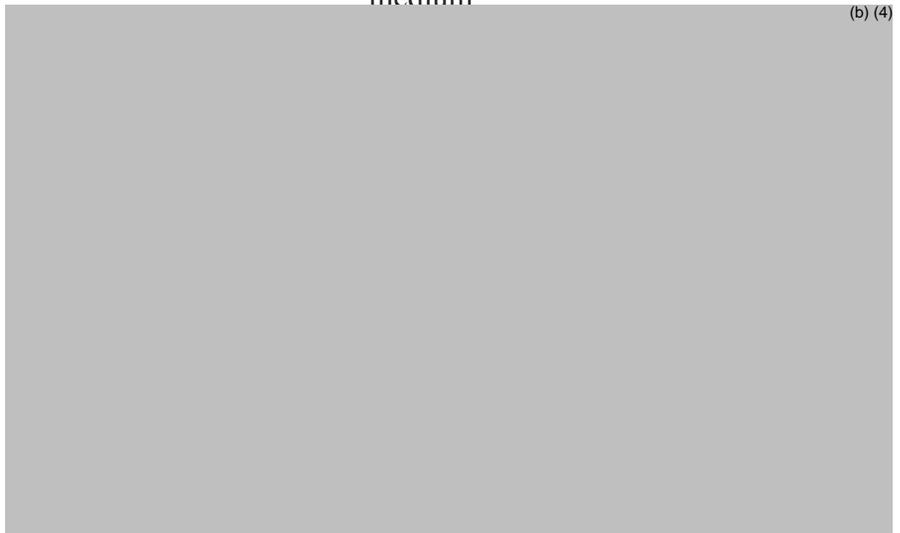
Apparatus:

Due to the observed (b) (4) rpm setting, the Applicant selected basket apparatus for the proposed Ceritinib tablets.

Rotation Speed:

The Applicant compared two agitation speed settings in the basket apparatus and selected agitation speed of 75 rpm based on the dissolution profiles of 375 mg batch (b) (4) in Figure 2.

Figure 2. Dissolution profiles with basket apparatus and varying agitation speeds in pH 2 medium



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Reviewer’s Assessment:

The Applicant’s selection of the rotation speed of 75 rpm (in USP I basket) is acceptable considering the comparable (or milder) dynamic condition to the approved dissolution condition (USP II (Paddle) at 60 rpm) for ZYKADIA® (Ceritinib) Capsules in NDA 205755.

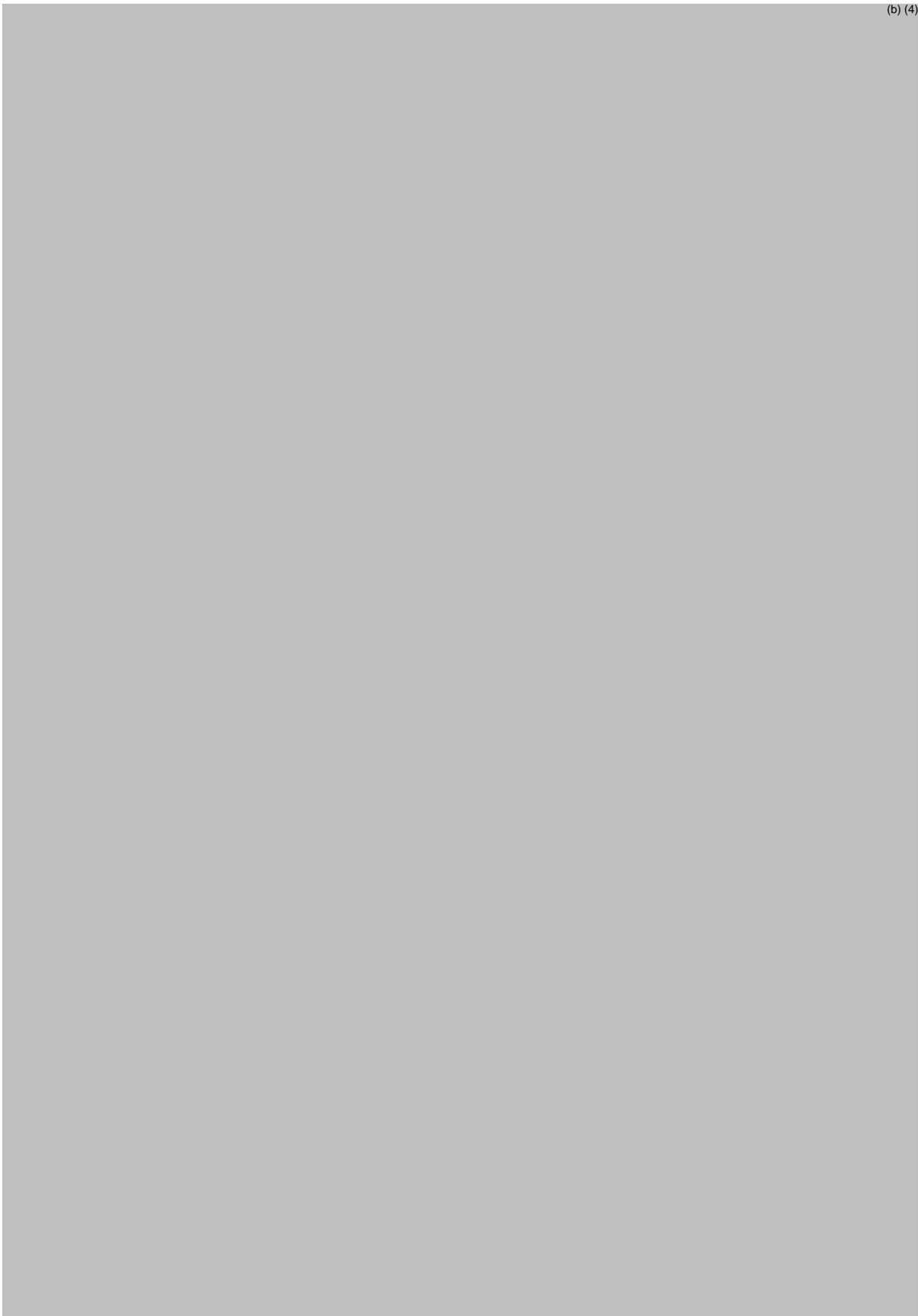
Dissolution Method Validation:

The Applicant provided the dissolution by UV validation report (<\\cdsesub1\evsprod\nda211225\0000\m3\32-body-data\32p-drug-prod\ldk378-fct\32p5-contr-drug-prod\32p53-val-analyt-proc\val-dissoln-uv.pdf>), which shows the method was validated for specificity, precision, linearity, accuracy, range, stability, filter and robustness. The CMC reviewer will review the validation results.

Discriminating Power of the Dissolution Method:

For the discriminatory power of the proposed dissolution method, the Applicant evaluated the following critical process parameters and material attributes:





Reviewer's Assessment:

Based on the provided information, the proposed dissolution method, i.e. 900 ml 0.01 HCl (pH 2) using USP I (Basket) at 75 RPM is adequately justified. Therefore, the proposed dissolution method is acceptable for the QC dissolution testing of the proposed drug product.

The discriminating power of the proposed dissolution method with regards to process parameters and DS particle size is limited, (b) (4)

Dissolution Acceptance Criterion:

The Applicant proposed the dissolution acceptance criterion of Q= (b) (4) % at (b) (4) minutes using the proposed dissolution method.

Based on the dissolution data of registration batches (X165LM (Biobatch), X163LM and X164 AN) shown in Figures 7-9 ((b) (4) % release in (b) (4) minutes), this Reviewer recommended a dissolution acceptance criterion of $Q = \frac{(b) (4)}{(4)} \% (Q)$ at 15 minutes for the proposed drug product. The recommended acceptance criterion was conveyed to the Applicant during the review cycle and was agreed upon on December 7, 2018 ([Appendix II](#))

(b) (4)



Zhuojun
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