CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205755Orig1s000

CHEMISTRY REVIEW(S)

Zykadia (ceritinib) Capsules

NDA 205755

Summary Basis for Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover
NJ 07936

Indication: For the treatment of patients with [redacted] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [redacted] (b) (4) with an anaplastic lymphoma kinase (ALK) inhibitor.

Presentation: The product will be available as 150 mg strength capsules. The capsules are blue-white colored hard gelatin capsules. The capsules are packaged in 175 ml HDPE bottles with 70-count in each bottle.

EER Status: Overall recommendation is "Acceptable" as of 27-Mar-2014.

Consults: ONDQA Biopharmaceutics - Acceptable (Okponanabofa Eradiri, 25-Mar-2014).

Microbiology - Acceptable (Jessica Cole, 18-Mar-2014)

Methods Validation - Pending

EA – Categorical exclusion granted.

Post-Approval Agreements: The applicant has agreed to provide the following information post approval.

- Novartis agrees to submit a revised testing monograph (TM) that will include a [redacted] (b) (4) method and specification for LDK378 drug product (capsule content) as post-approval commitment. The updated TM will be submitted by 30-April-2014.

- Novartis will submit the 9 months stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023).The updated stability data will be submitted by 16-May-2014.

Drug Substance:

The drug substance, ceritinib, a new molecular entity, is a white to almost white or light yellow powder [redacted] The drug substance synthesis is a [redacted] The structure of the drug substance was adequately established using appropriate analytical techniques.

The drug substance quality is ensured through quality control of all starting materials, in-process controls throughout the manufacturing process, appropriate quality control of the [redacted] and the appropriate final drug substance specification. The drug substance acceptance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., description, identification, assay, impurities, particle size distribution, residual solvents, and heavy metals, [redacted] and microbial controls. Because of the subjective nature of the acceptance criteria for the color of the powder, the specification also includes a control for the color of the solution. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of [redacted] months when stored under controlled room temperature.

Drug product:

Zykadia (ceritinib) capsules are an immediate release product to be marketed as 150 mg strength. The drug product formulation uses standard compendial excipients. These are microcrystalline cellulose, [redacted] hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and colloidal [redacted] The manufacturing process includes [redacted] followed by encapsulation. The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for description, identification, assay, uniformity of dosage units, degradation products, dissolution, and microbial controls. All analytical procedures for the drug product are adequately described and validated. An expiration period of 18 months is granted for the product.

The drug product is stored at 25°C with excursions permitted 15-30ºC (59-86ºF).

Conclusion: Adequate from CMC perspective.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application. Although the method validation of analytical procedures by the FDA laboratory is not complete at this point, it is not an approvability issue.

Overall Conclusion: The application is recommended for **"Approval"** from CMC perspective.

Ramesh K. Sood, Ph.D.
Acting Director, DPA I/ONDQA

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/s/

RAMESH K SOOD
04/08/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 2, 2014

FROM: Donghao (Robert) Lu, Ph.D.
Zhe (Jean) Tang, Ph.D.
Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment

TO: File NDA 205755

SUBJECT: OC recommendation

RECOMMENDATION: The drug product, Zykadia (Ceritinib) Capsule 150 mg, is recommended as APPROVAL from a CMC perspective – an overall "Acceptable" recommendation from the Office of Compliance has been issued and dated March 27, 2014.

REVIEW NOTE:

The NDA 205-755 CMC review #1 dated March 26, 2014 was completed. The review indicated that all other CMC issues have been resolved, except the pending overall recommendation from the Office of Compliance (OC) on manufacturing facilities. However, on March 27, 2014, OC issued "Acceptable" overall recommendation for the NDA. The EES summary report is shown below.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 205755/000
Org. Code: 107
Priority: 1
Stamp Date: 24-DEC-2013
PDUFA Date: 24-AUG-2014
Action Goal:
District Goal: 24-APR-2014

Sponsor: NOVARTIS PHARMS
1 HEALTH PLAZA BLDG 339 RM 1113
EAST HANOVER, NJ 079361080
Brand Name: CERITINIB (LDK378)
Estab. Name:
Generic Name: CERITINIB (LDK378)
Product Number; Dosage Form; Ingredient; Strengths
001; CAPSULE; CERITINIB; 150MG

FDA Contacts:				
	Z. TANG	Prod Qual Reviewer		3017964956
	J. COLE	Micro Reviewer		3017965148
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	L. ZHOU	Team Leader		3017961781

Overall Recommendation:	ACCEPTABLE	on 27-MAR-2014	by R. WITTORF	()	2404023113
	PENDING	on 14-JAN-2014	by EES_PROD		
	PENDING	on 14-JAN-2014	by EES_PROD		
	PENDING	on 14-JAN-2014	by EES_PROD		

Establishment: **CFN:** 9611204 **FEI:** 3002807772
NOVARTIS PHARMA AG
LICHTSRASSE 35
BASEL, , SWITZERLAND
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE OTHER TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-MAR-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9612715 **FEI:** 3002807776
NOVARTIS PHARMA AG
CORK
RINGASKIDDY, CORK, , IRELAND
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE STABILITY TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 14-JAN-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9692042 **FEI:** 3002865753		
	NOVARTIS PHARMA STEIN AG ROTHAUSWEG		
	SCHWEIZERHALLE, BASEL-LANDSCHAFT, SWITZERLAND		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 9692043 **FEI:** 3002653483

NOVARTIS PHARMA STEIN AG
SCHAFFHAUSERSTRASSE 101

STEIN, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: (b) (4)

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 2416082 **FEI:** 2416082

NOVARTIS PHARMACEUTICALS CORP

SUFFERN, , UNITED STATES 10901

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-JAN-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

DONGHAO R LU
04/02/2014

ZHE J TANG
04/03/2014

ALI H AL HAKIM
04/03/2014

NDA 205755

Zykadia™ (Ceritinib) Capsules

Novartis Pharmaceuticals Corporation

Review of Drug Product Sections

Z. Jean Tang

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA
For the Division of Drug Oncology Products 2

Table of Contents

CMC Review Data Sheet

1. NDA 205755

2. REVIEW #: 1

3. REVIEW DATE: 04-Feb-2014

4. REVIEWER: Z. Jean Tang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 109272 submission	08-Oct-2010
Original IND 109272 CMC review	11-Nov-2012
CMC-only pre-NDA type B meeting preliminary comments	13-May-2013
CMC-only pre-NDA type B meeting	14-May-2013

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 205-755	24-Dec-2014
NDA 205-755 (Amendment 031, CMC response)	12-MAR-2014
NDA 205-755 (Amendment 032, CMC response)	13-MAR-2014
NDA 205-755 (Amendment 038, CMC response)	21-MAR-2014
NDA 205-755 (Amendment 042, CMC responses)	28-MAR-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative:	Yanina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs
Telephone:	862-778-1767

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zykadia™ Capsules
b) Non-Proprietary Name: Ceritinib Capsules

c) Code Name/# (ONDQA only): LDX378
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1 (new molecular entity)
- Submission Priority: Expedite Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: ATP-competitive inhibitor of anaplastic lymphoma kinase activity

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 150 mg

13. ROUTE OF ADMINISTRATION: oral

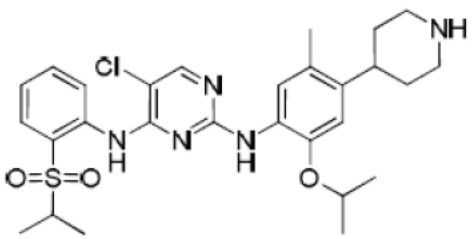
14. Rx/OTC DISPENSED: __√__Rx ___OTC

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:

Chemical structure	
Molecular formula	$C_{28}H_{36}ClN_5O_3S$
Molecular weight	558.14
United States Adopted Name (USAN)	Not yet established
CAS Chemical name	5-Chloro-N^4-[2-[(1-methylethyl)sulfonyl]phenyl]-N^2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine
Chemical Abstracts Service (CAS) registry number	1032900-25-6
Novartis Laboratory Code	LDK378

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	COMMENTS
(b) (4)	IV	(b) (4)		4	7	N/A
	III			4	7	N/A
	III			4	7	N/A
	III			4	7	N/A
	III			4	7	N/A
	III			4	7	N/A
	III			4	7	N/A

[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 – per section III.G of the "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics," "Policy on the Review of Container Closure Systems for Solid Oral Drug Products," and MAPP 5015.5
8 – 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109272	Treatment of Subjects with Advanced Solid Tumors

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	27-Mar-2014	
Methods Validation	Validation request *	18-MAR-14	Lu and Tang
ODS DMEPA	Acceptable	24-MAR-14	Otto L. Townsend
EA	Acceptable	3-MAR-14	Donghao Lu
Biopharm	Acceptable	25-MAR-14	Okpo Eradiri
Pharm/Tox	Acceptable	25-MAR-14	Margaret Brower
Micro Consultation	Acceptable	18-MAR-14	Jessica Cole
EES	Acceptable	27-Mar-2014	Robert Wittorf

* Methods Validation request has been sent to St. Louis lab (FDA/DPA). The approvability of this NDA is independent on the validation results. (per IQP)

The CMC Review for NDA 205755

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product, Zykadia (Ceritinib) Capsule 150 mg, is recommended for APPROVAL from a CMC perspective.

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

- **Novartis agrees to submit a revised testing monograph (TM) that will include a (b) (4) method and specification for LDK378 drug product (capsule content) as post-approval commitment. The updated TM will be submitted by 30-April-2014.**

- **Novartis will submit the 9 months stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023).The updated stability data will be submitted by 16-May-2014.**

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance is Ceritinib. The chemical name is 5-Chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine. It has a molecular formula of $C_{28}H_{36}ClN_5O_3S$ and its molecular weight is 558.14.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The synthesis route (b) (4) appear adequate for the manufacturing of the ceritinib drug substance. Science and risk based approaches were applied during CMC evaluation to make the regulatory decisions on manufacturing control strategies.

The impurities detected during the synthesis and development of the drug substance were evaluated. Analytical methods were developed for the control of the impurities

listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level were adequately presented. Science and risk based approaches were applied during CMC evaluation to make the regulatory decisions on impurity control strategies.

Ceritinib was studied for its stability under the ICH stability test conditions. The drug substance was physically and chemically stable based on evaluation of the testing data. The drug substance has a retesting period of (b) (4) months. Science and risk based approaches were applied during CMC evaluation to make the regulatory decisions on stability data acceptance.

(2) Drug Product

The drug product is an immediate release hard gelatin capsule for oral administration for the treatment of tumors characterized with genetic abnormalities in anaplastic lymphoma kinase (ALK), including non-small cell lung cancer (NSCLC).

The drug product contains 150 mg LDK378 (Ceritinib) formulated using excipients meeting pharmacopoeia quality standards. The manufacturing process of LDK378 150 mg hard gelatin capsule consists of (b) (4) The final (b) (4) is encapsulated in the blue and white hard gelatin capsules.

The Novartis provided two stability studies for 150 mg Ceritinib hard gelatin capsules. One supportive study contains two batches that were manufactured during the development and used in the clinical studies, which provided stability data up to 24 months for one batch and 12 months for another batch. The registration stability contains three batches that are representative of the final manufacturing process and support the intended to be marketed product. The registration stability study covers stability data up to 6 months. Novartis anticipates that the updated stability data up to 9 months for the 3 registration stability batches and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023) being available by mid May 2014. However, the registration and supportive stability studies have been performed using the (b) (4) Ceritinib 150 mg hard gelatin capsule, which was the color of the capsule shell during early and late development and is deferent as used in the commercial product (blue and white hard gelatin capsules). Novartis will perform additional bridging stability studies on 3 additional blue-white color capsule batches (batches X398IK, X399IK and X400IK) manufactured at the commercial site using the commercial manufacturing process. Based on the current available stability data using science and risk management approaches, 18 months shelf life for Ceritinib 150 mg hard gelatin capsule stored at 25 °C (77 °F) in tight containers is granted.

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

Ceritinib (LDK378) is an ATP-competitive inhibitor of anaplastic lymphoma kinase (ALK) activity. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated

phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*. The drug product is used for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

The recommended dose is 750 mg taken orally once daily. Take the drug product with an empty stomach. Temporary dose interruption and/or dose reduction (by decrements of 150 mg) may be required based on individual safety and tolerability. The product should be stored at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F). The product has an expiration period (shelf life) of 18 months.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The Microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Zykadia.

A method validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis, and the results are still pending. The approvability of this NDA is independent on the validation results.

From a CMC perspective, Novartis has submitted sufficient and appropriate information to support the approval of the drug product. Novartis has also adequately addressed the CMC comments during the review process. Their responses and the CMC evaluations for these responses are described at the end of this document.

The Office of Compliance has issued an overall recommendation of acceptable for the inspections of the manufacturing and testing facilities for the drug substance and drug product.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Zhe Jean Tang, Ph.D, Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Ali Al Hakim, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

ZHE J TANG
04/03/2014

ALI H AL HAKIM
04/03/2014

NDA 205-755

Zykadia (Ceritinib)
Capsule
150 mg

Novartis Pharmaceuticals Corporation

Drug Substance Review

Division of Oncology Drug Products

Donghao (Robert) Lu, Ph.D.
Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 205-755

2. REVIEW NUMBER: 1

3. REVIEW DATE: 21 MARCH 2014

4. REVIEWER: Donghao (Robert) Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
Original IND 109272 submission	Oct-2010
Original IND 109272 CMC review	Nov-2012
CMC-only pre-NDA type B preliminary comments	May-2013
CMC-only pre-NDA type B meeting	May-2013

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 205-755	24-Dec-2014
NDA 205-755 (Amendment 029, CMC response)	12-MAR-2014
NDA 205-755 (Amendment 030, CMC response)	13-MAR-2014
NDA 205-755 (Amendment 036, CMC response)	21-MAR-2014

7. NAME & ADDRESS OF APPLICANT:

NAME:	**Novartis Pharmaceuticals Corporation**
ADDRESS:	**One Health Plaza, East Hanover, NJ 07936**
REPRESENTATIVE:	**Yanina Gutman, PharmD., Senior Associate Director, Drug Regulatory Affairs**
TELEPHONE:	**862-778-1767**

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**Zykadia (Ceritinib)**
NON-PROPRIETARY NAME (USAN)	**Ceritinib**
CODE NAME/ NUMBER (ONDC ONLY)	**LDK378**
CHEMISTRY TYPE / SUBMISSION PRIORITY	**1P (Expedite Priority)**

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: ATP-competitive inhibitor of anaplastic lymphoma kinase activity

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 150 mg

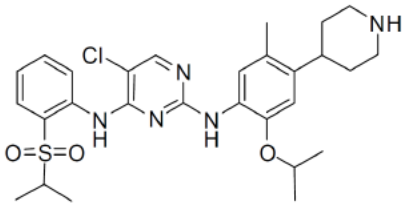
13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__x__Not a SPOTS product

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

Name (USAN, INN): Ceritinib
Name (CAS): 5-Chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine
Other Name: 5-Chloro-2-N-{5-methyl-4-(piperidin-4-yl)-2-[(propan-2-yl)oxy]phenyl}-4-N-[2-(propane-2-sulfonyl)phenyl]pyrimidine-2,4-diamine (IUPAC)
(CAS) Registry Num: 1032900-25-6
Mol. Formula: $C_{28}H_{36}ClN_5O_3S$
Mol. Wt.: 558.14
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLET

*** See DP review**

[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.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109272	

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	Validation request *	18-MAR-14	Lu and Tang
ODS DMEPA	Acceptable	24-MAR-14	Otto L. Townsend
EA	Acceptable	3-MAR-14	Lu and Tang
Biopharm	Acceptable	25-MAR-14	Okpo Eradiri
Pharm/Tox	Acceptable	25-MAR-14	Margaret Brower
Micro Consultation	Acceptable	18-MAR-14	Jessica Cole

* Methods Validation request has been sent to St. Louis lab (FDA/DPA). The approvability of this NDA is independent on the validation results. (per IQP)

The Chemistry Review for NDA 205-755

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product, Zykadia (Ceritinib) Capsule 150 mg, is recommended as APPROVAL from a CMC perspective, pending Office of Compliance's recommendation.

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

The specification and method qualification data for [redacted] (b) (4) of Ceritinib Capsule 150 mg will be provided post-approval.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is Ceritinib. The chemical name is 5-Chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine. It has a molecular formula of $C_{28}H_{36}ClN_5O_3S$ and its molecular weight is 558.14.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The synthesis route [redacted] (b) (4) are adequate for the manufacturing of the ceritinib drug substance. Science and risk based approaches were applied during CMC evaluation to make the regulatory decisions on manufacturing control strategies.

The impurities detected during the synthesis and development of the drug substance were evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level were adequately presented. Science and risk based approaches were applied during CMC evaluation to make the regulatory decisions on impurity control strategies.

Ceritinib was studied for its stability under the ICH stability test conditions. The drug substance was physically and chemically stable based on evaluation of the testing data. The drug substance has a retesting period of (b) (4) months. Science and risk based approaches were applied during CMC evaluation to make the regulatory decisions on stability data acceptance.

2. Drug Product

The drug product is an immediate release hard gelatin capsule for oral administration for the treatment of tumors characterized with genetic abnormalities in anaplastic lymphoma kinase (ALK), including non-small cell lung cancer (NSCLC).

The drug product contains 150 mg LDK378 (Ceritinib) formulated using excipients meeting pharmacopoeial quality standards. The manufacturing process of LDK378 150 mg hard gelatin capsule consists of (b) (4) The final (b) (4) is encapsulated in the blue and white hard gelatin capsules.

The Novartis provided two stability studies for 150 mg Ceritinib hard gelatin capsules. One supportive study contains two batches that were manufactured during the development and used in the clinical studies, which provided stability data up to 24 months for one batch and 12 months for another batch. The registration stability contains three batches that are representative of the final manufacturing process and support the intended to be marketed product. The registration stability study covers stability data up to 6 months. Novartis anticipates that the updated stability data up to 9 months for the 3 registration stability batches and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023) being available by mid May 2014. However, the registration and supportive stability studies have been performed using (b) (4) Ceritinib 150 mg hard gelatin capsule, which was the color of the capsule shell during early and late development and is deferent as used in the commercial product (blue and white hard gelatin capsules). Novartis will perform additional bridging stability studies on 3 additional blue-white color capsule batches (batches X398IK, X399IK and X400IK) manufactured at the commercial site using the commercial manufacturing process. Based on the current available stability data using science and risk management approaches, 18 months shelf life for Ceritinib 150 mg hard gelatin capsule stored at 25 °C (77 °F) in tight containers is granted.

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

Ceritinib (LDK378) is an ATP-competitive inhibitor of anaplastic lymphoma kinase (ALK) activity. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both in vitro and in vivo. The drug product is used for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

The recommended dose is 750 mg taken orally once daily. Take the drug product with an empty stomach. Temporary dose interruption and/or dose reduction (by decrements of 150 mg) may be required based on individual safety and tolerability. The product should be stored at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F). The product has an expiration period (shelf life) of 18 months.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The Microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Zykadia.

A method validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis, and the results are still pending. The approvability of this NDA is independent on the validation results.

From a CMC perspective, Novartis has submitted sufficient and appropriate information to support the approval of the drug product. Novartis has also adequately addressed the CMC comments during the review process. Their responses and the CMC evaluations for these responses are described at the end of this document.

The Office of Compliance has not issued an overall recommendation for the inspections of the manufacturing and testing facilities for the drug substance and drug product. Therefore, this NDA may not be approved until a final acceptable recommendation is made by the Office of Compliance.

III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ali H. Al Hakim, Ph.D.

C. CC Block

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/s/

DONGHAO R LU
03/26/2014

ALI H AL HAKIM
03/26/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet

1. OMPQ Reviewer: Robert H. Wittorf, PharmD.

2. NDA/BLA Number: 205755
   Submission Date: 24-Dec-2013
   21st C. Review Goal Date: TBD
   PDUFA Goal Date: 25-Apr-2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	TBD
Established or Non-Proprietary Name (USAN) and strength:	Ceritinib (LDK 378)
Dosage Form:	Immediate Release Capsules, 150 mg

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Novartis Pharmaceuticals Corporation
Responsible Organization (OND Division):	DOP 2

II. Application Detail

1. INDICATION: Treatment of patients with [redacted] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [redacted] (b) (4)
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 150 mg
4. Rx/OTC DISPENSED: X☐Rx ☐OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			
2.	Breakthrough Therapy Designation	X			25-Apr-2014 PDUFA action date (decided at 14-Jan-2014 planning meeting)
3.	Orphan Drug Designation	X			
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	x		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	x		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	x		356h form
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	x		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	x		
	2. Do comments in EES indicate a request to participate on inspection(s)?		x	
	3. Is this first application by the applicant?		x	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		x	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	x		NME
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?		x	
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	x		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		x	This manufacturing process is a (b) (4) [redacted]

Process flow chart/diagram (see eCTD Section 2.3.S.1): (next page)

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(b) (4)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		x	This is an immediate release capsule with (b) (4) encapsulation into a hard gelatin capsule.

(b) (4)

[redacted]

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

A review of the facilities in EES and FACTS was conducted. No facility-related risks were identified at the time of this review.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

All sites were reviewed for inspectional trends, product specific issues, and manufacturing processes. No inspectional issues were noted.

Additional information not covered above

This application has received priority review with a four month review window. Based on inspectional history of facilities, manufacturing process, and priority review status, PAIs have been waived. A post-approval inspection of the drug substance and drug product site is recommended.


(b) (4)

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) **Yes**
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) **No**

REVIEW AND APPROVAL

(DARRTS)

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/s/

ROBERT H WITTORF
01/22/2014

MAHESH R RAMANADHAM
01/22/2014

PRODUCT QUALITY (Small Molecule)
FILING REVIEW and IQA FOR NDA ~~or Supplement~~ (ONDQA)

NDA Number:
205755

Supplement Number and Type:

Established/Proper Name:
Ceritinib Capsules

Applicant:
Novartis Pharmaceuticals Corparation

Letter Date:
December 24, 2012
(~~Resubmission~~)

Stamp Date:
December 24, 2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	Yes		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Yes		
3.	Are all the pages in the CMC section legible?	Yes		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Yes		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Yes		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		EER Request by ONDQA project Manager, Jewell Martin
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	Yes		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	Yes		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	Yes		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	Yes		Also refer to CMC pre-NDA meeting package meeting min. and
14.	Does the section contain information regarding the characterization of the DS?	Yes		
15.	Does the section contain controls for the DS?	Yes		
16.	Has stability data and analysis been provided for the drug substance?	Yes		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		No	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		No	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	Yes		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	Yes		
21.	Is there a batch production record and a proposed master batch record?	Yes		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Yes		
23.	Have any biowaivers been requested?			Fileable from ONDQA Biopharm. Refer to Biopharm filing review
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Yes		
25.	Does the section contain controls of the final drug product?	Yes		
26.	Has stability data and analysis been provided to support the requested expiration date?	Yes		Review issue
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		No	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	Yes		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	Yes		Capsule. No test is proposed

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	Yes		LOAs provided for DMFs (b) (4)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	Yes		
33.	Have the immediate container and carton labels been provided?	Yes		

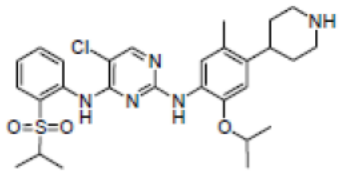
J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	Yes		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		No	No CMC fileability

36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		No	

Note:
Ceritinib (LDK378) is an oral, [redacted] (b) (4) ALK kinase inhibitor. ALK is a receptor tyrosine kinase involved in the genesis of several cancers through genetic aberrations involving translocation of the kinase domain with multiple fusion partners or activating mutations in the fulllength receptor that result in ligand-independent constitutive activation. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both in vitro and in vivo. The ceritinib clinical development program is ongoing under IND109272 (ceritinib alone) [redacted] (b) (4)

Proposed Indication: for the treatment of patients with [redacted] (b) (4) metastatic NSCLC who have [redacted] (b) (4)

Structural formula:



Molecular formula and Molecular weight :

$C_{28}H_{36}ClN_5O_3S$

558.14

LDK378 drug substance is manufactured by a [redacted] (b) (4)

[redacted] (b) (4)

LDK378 drug product is a hard gelatin capsule formulation [redacted] 150 mg strength 150 mg strength was finally selected and its proposed the acceptance criteria appear to be acceptable during the stability study. No other significant increase of total degradation products was observed. Clinical formulation of LDK378 150 mg was stable up to 24 months at proposed storage conditions which was selected for the clinical development of LDK378 150 mg hard gelatin capsule. During further development, the qualitative and quantitative composition of LDK378 150 mg hard gelatin capsule remained unchanged. Only, the [redacted] generic hard-gelatin capsule shell was replaced by the final commercial blue opaque -white opaque colored hard-gelatin capsule shell

Please note that this DP is given as a Breakthrough Therapy Designation status on March 6, 2013. In addition, during pre-NDA meeting, it was agreed that the applicant submits [redacted] month time point DS stability data (e.g 2 batches) in the original NDA submission.
The proposed DP expiry [redacted] is requested based on supportive 24 month stability data and other supporting stability data during earlier clinical development batches.

Comments:
The following points may need to have review team input before sending IR letter:

For example,

- the USAN Council approval letter for USAN name [redacted] and
- test results for DP particle size [redacted] pending ONDQA Biopharm input
- acceptance criteria for any unspecified impurities [redacted] and total unspecified impurities.

Liang Zhou *1-20-2014*

Name of
CMC Lead / ~~CMC Reviewer~~ Date
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

*{*Ali Al Hakim*}* *1-20-2014*

Name of
Branch Chief Date
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

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/s/

LIANG ZHOU
01/21/2014

ALI H AL HAKIM
01/21/2014