CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211225Orig1s000

OTHER REVIEW(S)

DOP2 Associate Director for Labeling Review

Product Title	**Zykadia (ceritinib) tablets, for oral use**
Applicant	Novartis
Application/Supplement Number	NDA 211225
Type of Application/Submission[1]	Orignal NDA
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	None
Approved Indication(s) (if applicable)	Anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC)
Date FDA Received Application	May 18, 2018
Review Classification (Priority/Standard)	Standard
Action Goal Date	March 18, 2019
Review Date	February 15, 2019
Reviewer	Stacy S Shord, Pharm.D.

Background:
The applicant is seeking approval of a new dosage form and submitted a labeling document with revisions to the currently approved labeling for the drug product: ZYKADIA (ceritinib) capsules, for oral use. The capsule drug product was initially approved on April 29, 2014 under NDA 205755. The applicant amended the approved labeling to include information specific to the new tablet formulation, food effects, and drug interactions.

Labeling Review:
The approved labeling document was reviewed to help ensure that product information (PI):

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[2]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

The attached PI contains the working version of the ZYKADIA labeling with my recommended edits and comments (identified by my initials) and includes comments and edits from other review team members. My labeling recommendations provided in this review (e.g., recommended edits and comments regarding parts of PI) should be considered preliminary and may not represent final recommendations for the ZYKADIA labeling.

[1] Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

[2] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.

[3] See *PLR Requirements for PI* website for PLR labeling guidances.

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/s/

STACY S SHORD
02/27/2019 09:06:23 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 15, 2019
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211225
Product Name and Strength:	Zykadia (ceritinib) Tablets, 150 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corp. (Novartis)
FDA Received Date:	January 7, 2019 and February 6, 2019
OSE RCM #:	2018-1108-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

This memo evaluates the January 7, 2019 container label and professional sample carton labeling and the February 6, 2019 revised professional sample container label for Zykadia (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

We previously recommended that the expiration date appear in YYYY-MM-DD or YYYY-MMM format for the commercial container label, professional sample container label, and carton labeling; however, Novartis stated they intend to use the expiration date format of "MMM YYYY (e.g., DEC 2021)". Thus, Novartis did not revise the previously reviewed January 7, 2019 container label and professional sample carton labeling. Since the proposed expiration date format will use alphabetical characters to express the month and numerical characters to express the year, we find their proposed expiration date format acceptable.

[a] Little, C. Label and Labeling Review for Zykadia (NDA 211225). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 14. RCM No.: 2018-1108.

Novartis addressed most of our recommendations for the professional sample container label but did not implement the recommendation to present all product storage information on the same panel. Novartis stated "decreasing the font size...would impact legibility." Given the 5-point font size on the physician sample container label is already smaller than the FDA recommended 12-point font, we agree further decreasing the font will impact legibility. Thus, the proposed presentation of the product storage information on the February 6, 2019 revised professional sample container label is acceptable.

3 CONCLUSION

The January 7, 2019 container label and professional sample carton labeling and the February 6, 2019 revised professional sample container label for Zykadia are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 6, 2019

Container labels

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/s/

COLLEEN L LITTLE
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CHI-MING TU
02/15/2019 08:18:35 AM

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: January 25, 2019

TO: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)
Office of New Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Pharmaceutical Product Development (PPD), Austin, TX.

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of studies CLDK378A2107, CLDK378A2121, and CLDK378A2122 (NDA 211225) conducted at PPD, Austin, TX.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision.

2 Inspected Studies:

Study Number: CLDK378A2107
Study Title: "A randomized, open-label, two-cohort, two-period crossover study to assess the bioequivalence

between ceritinib FMI tablets and ceritinib FMI capsules at 750 mg (2 x 375 mg tablets vs. 5 x 150 mg capsules; 5 x 150 mg tablets vs. 5 x 150 mg capsules) in healthy subjects under fasted state”

Dates of conduct: 03/30/2016 (first subject first visit) – 08/23/2016 (last subject last visit)

Study Number: CLDK378A2121
Study Title: “A randomized, open-label, three-period, six-sequence crossover study to assess the relative bioavailability of 750 mg ceritinib tablets (2 x 375 mg tablets) administered with either a low-fat low-calorie or high-fat high calorie meal compared to under fasting condition in healthy subjects”

Dates of conduct: 01/03/2017 (first subject first visit) – 03/16/2017 (last subject last visit)

Study Number: CLDK378A2122
Study Title: “A randomized, open-label, two-cohort, two-period crossover study to assess the bioequivalence between ceritinib FMI tablets and ceritinib FMI capsules at 450 mg (3 x 150 mg tablets vs. 3 x 150 mg capsules) and 600 mg (2 x 300 mg tablets vs. 4 x 150 mg capsules) in healthy subjects under fed state”

Dates of conduct: 01/04/2017 (first subject first visit) – 04/03/2017 (last subject last visit)

Clinical site: PPD
7551 Metro Center Drive, Suite 200
Austin, TX

ORA investigator Leighton K Ngai inspected PPD, Austin, TX from October 29 to November 2, 2018.

The inspection included a thorough examination of study records, including inclusion/exclusion criteria, safety & data monitoring, test article accountability, institutional review board approvals, sponsor's correspondence with the principal investigators, informed consent forms, protocol compliance, audit trials of electronic case report forms, and adverse event reports.

3 Inspectional Findings

At the conclusion of the inspection, Investigator Ngai did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. There were also no discussion items.

4. Conclusion:

After reviewing the inspectional findings, I conclude the data from studies CLDK378A2107, CLDK378A2121, and CLDK378A2122 (NDA 211225) are reliable for Agency review.

Based on the inspectional findings, studies of similar design conducted between the previous inspection (May/June 2016) and the end of the current surveillance interval should be considered reliable without an inspection.

Melkamu Getie-Kebtie, Ph.D., R.Ph.
Pharmacologist

Final Classification:

NAI - PPD
Austin, TX
FEI#: 3011410938

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Getie-Kebtie
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: MG 1/22/2019, 1/24/2019
Edit: SA 1/22/2019, 1/24/2019; JC 1/25/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/PPD, Austin, TX, USA

OSIS File #: BE 8191

FACTS: 11865492

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/s/

MELKAMU GETIE KEBTIE
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STANLEY AU
01/25/2019 02:17:25 PM
Team Lead

SEONGEUN CHO
01/25/2019 02:25:33 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 14, 2019
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211225
Product Name and Strength:	Zykadia (ceritinib) Tablets, 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corp.
FDA Received Date:	December 7, 2018 and January 7, 2019
OSE RCM #:	2018-1108
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of this NDA, this review evaluates the proposed Zykadia prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors.

Zykadia (ceritinib) capsules, 150 mg, were approved under NDA 205755 on April 29, 2014. Novartis Pharmaceuticals Corp. (Novartis) now seeks approval for the new dosage formulation, tablets, under NDA 211225. Novartis proposes to utilize one PI for both dosage formulations of Zykadia. Per the Novartis' June 5, 2018 request for proprietary name review submission, the proposed tablets are a bioequivalent replacement for the currently marketed capsules and that they do not intend to maintain both dosage formulations on the US market. Novartis states, "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."

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Novartis currently markets Zykadia capsules in 70-count bottles and seeks approval to market the proposed Zykadia tablets in 84-count bottles. We note the proposed package size will provide a 28-day supply of medication based on the recommended daily dose for Zykadia (3 capsules or 3 tablets once daily). Therefore, we find the proposed 84-count bottles acceptable from a medication error perspective.

Our review found the proposed Zykadia PI, commercial container label, professional sample container label, and professional sample carton labeling may be improved to promote safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

The proposed PI, commercial container label, professional sample container label, and professional sample carton labeling for Zykadia may be improved to promote safe use of the product as described in Section 4.1 and Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. How Supplied/Storage and Handling Section
        a. As presented, the storage information for both dosage formulations are presented in an inconsistent format (i.e., "Store at 25°C (77°F)" vs. "Store at 20°C to 25°C (68°F to 77°F)"). We recommend presenting this information in a consistent format (i.e., temperature range) for both dosage formulations to minimize the risk for product storage errors and confusion. We defer to the Review Team for the appropriate presentation of the storage information for both dosage formulations.

4.2 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORP.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments for Commercial Container labels & Carton Labeling
    1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Physician Sample Container Labels
    1. Identify the location and header of the lot number in accordance with 21 CFR 201.10(i).
    2. We strongly encourage including the expiration date on the professional sample container label.Error! Bookmark not defined.

3. If space permits, relocate the last part “Room Temperature].” of the statement “Store at… [See USP Controlled…” to appear on the same panel.
4. Consider decreasing the prominence of the net quantity statement (i.e., 21 Tablets) and “Rx only” statement to ensure important product identifying information (i.e. product name, product strength) is most prominent on container labels.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zykadia received on December 7, 2018 from Novartis Pharmaceuticals Corp.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Zykadia</th></tr>
<tr><td>Initial Approval Date</td><td>N/A (Zykadia capsules approved on April 29, 2014)</td></tr>
<tr><td>Active Ingredient</td><td>ceritinib</td></tr>
<tr><td>Indication</td><td>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.</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>Current
Capsules
Proposed
Tablets</td></tr>
<tr><td>Strength</td><td>150 mg</td></tr>
<tr><td>Dose and Frequency</td><td>450 mg orally once daily with food until disease progression or unacceptable toxicity
Dose Reductions<table><tr><th>Dose Reduction Schedule</th><th>Dose Level</th></tr><tr><td>Starting dose</td><td>450 mg taken orally once daily with food</td></tr><tr><td>First dose reduction</td><td>300 mg taken orally once daily with food</td></tr><tr><td>Second dose reduction</td><td>150 mg taken orally once daily with food</td></tr></table></td></tr>
<tr><td>How Supplied</td><td>Current (capsules)
70-count bottles
Proposed (tablets)
84-count bottles for commercial use
21-count physician sample bottles</td></tr>
<tr><td>Storage</td><td>Current (capsules)
Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)
Proposed (tablets)
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)</td></tr>
<tr><td>Container Closure</td><td>HDPE bottle (b) (4)</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 31, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Zykadia and ceritinib. Our search identified 1 previous review[a] since the date of our last search[b], and we confirmed that our previous recommendations were implemented.

[a] Stewart, J. Label and Labeling Review for Zykadia (NDA 205755/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 15. RCM No.: 2017-2470.

[b] Date of last search on December 14, 2017 in Stewart, J. Label and Labeling Review for Zykadia (NDA 205755/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 15. RCM No.: 2017-2470.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 31, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Any of the Words: Zykadia ceritinib

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Zykadia.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Zykadia labels and labeling submitted by Novartis Pharmaceuticals Corp.

- Container Label received on January 7, 2019
- Professional Sample Container Label received on January 7, 2019
- Professional Sample Carton Labeling received on January 7, 2019
- Prescribing Information (Image not shown) received on December 7, 2018

G.2 Label and Labeling Images

Container Label

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Professional Sample Container Label

Professional Sample Carton Labeling

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01/14/2019 01:38:10 PM

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: 9/13/2018

TO: Division of Oncology Products (DOP2)
Office of Hermatology and Oncology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 211225

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is, OSIS recently inspected the site listed below and the inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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/s/

SHILA S NKAH
09/13/2018