

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211225Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

# Office of Clinical Pharmacology Review

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<b>NDA or BLA Number</b>	<i>NDA 211225</i>
<b>Link to EDR</b>	<i>\\CDSESUBI\evsprod\NDA211225</i>
<b>Submission Date</b>	<i>May 18, 2018</i>
<b>Submission Type</b>	<i>Standard review</i>
<b>Brand Name</b>	<i>ZYKADIA</i>
<b>Generic Name</b>	<i>Ceritinib</i>
<b>Dosage Form and Strength</b>	<i>Film-coated tablets at 150 mg</i>
<b>Route of Administration</b>	<i>Oral administration</i>
<b>Proposed Indication</b>	<i>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.</i>
<b>Applicant</b>	<i>Novartis Pharmaceutical Corporation</i>
<b>Associated IND</b>	<i>NDA 205755</i>
<b>OCP Reviewer</b>	<i>Xiling Jiang</i>
<b>OCP Team Leader</b>	<i>Hong Zhao</i>

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## 1. EXECUTIVE SUMMARY

The Applicant is seeking approval of a new dosage form for ZYKADIA® (ceritinib), 150 mg film-coated tablet (FCT) as a bioequivalent, interchangeable formulation for ZYKADIA® (ceritinib) 150 mg hard gelatin capsule (HGC), currently approved 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.

The results of the three bioavailability/bioequivalence studies demonstrated that the proposed tablet formulation is bioequivalent (BE) to the approved 150 mg capsule formulation supporting the approval of the proposed 150 mg tablet formulation.

### 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211225. This NDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	<p>The primary evidence of effectiveness comes from bioequivalence (BE) studies CLDK378A2107 and CLDK378A2122 in the healthy subjects. BE was demonstrated between tablet and capsule formulations under both fasted conditions and fed condition (a low-fat low-calorie meal).</p> <p>The food effect study CLDK378A2121 reported numerically less food effect on tablet formulation following both a high-fat high-calorie meal and a low-fat low-calorie meal, when comparing to the results of capsule formulation from historical data.</p>
General dosing instructions	The proposed dosing regimen is 450 mg orally once daily with food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Refer to Ceritinib label, as ceritinib is an approved drug.
Labeling	<p>-----DOSAGE FORMS AND STRENGTHS-----</p> <p>Capsules: 150 mg Tablets: 150 mg</p> <p>A food effect study conducted in healthy subjects with a single 750 mg (b) (4) dose of ZYKADIA (tablets) showed that a high-fat meal (containing approximately 1000 calories and 58 grams of fat) increased ceritinib AUC by 64% and Cmax by 58% and a low-fat meal (containing approximately 330 calories and 9 grams of fat) increased ceritinib AUC by 39% and Cmax by 42% as compared with the fasted conditions.</p> <p>Additional editorial changes in sections 7.1 and 12.3.</p> <p>Generally acceptable.</p>

Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed 150 mg tablet formulation is BE to the approved 150 mg capsule formulation in two BE studies CLDK378A2107 and CLDK378A2122.
Other (specify)	None.

## 1.2 Post-Marketing Requirements and Commitments

Not applicable, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Clinical Pharmacology evaluated three bioavailability/bioequivalence studies included in this NDA submission, which aimed to support the approval of a new dosage form for ceritinib, 150 mg FCT as a bioequivalent and interchangeable formulation for ceritinib 150 mg HGC, currently approved for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.

### 2.1 Pharmacology and Clinical Pharmacokinetics

Ceritinib (LDK378; trade name: Zykadia®) is an orally administered, selective inhibitor of anaplastic lymphoma kinase (ALK) auto-phosphorylation, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells.

Ceritinib is approved for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is ALK-positive. refer to Ceritinib labeling for detailed information about clinical pharmacokinetics.

### 2.2 Dosing and Therapeutic Individualization

#### *2.2.1 General dosing*

The proposed dosing regimen is 450 mg orally once daily with food.

#### *2.2.2 Therapeutic individualization*

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

### 2.3 Outstanding Issues

None.

## 2.4 Summary of Labeling Recommendations

The following are recommended major changes to the proposed ceritinib labeling change:

### Prescribing information

- DOSAGE FORMS AND STRENGTHS: Remove statements about [REDACTED] (b) (4) [REDACTED] as this is not appropriate to include in labeling.

### Other Prescription Drug Labeling

- 3. DOSAGE FORMS AND STRENGTHS: Remove statements about [REDACTED] (b) (4) [REDACTED] as this is not appropriate to include in labeling.
- 12.3 Pharmacokinetics: Remove statements about [REDACTED] (b) (4) [REDACTED] as this is not appropriate to include in labeling.

## 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

### 3.1 Overview of the Product and Regulatory Background

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

### 3.2 General Pharmacology and Pharmacokinetic Characteristics

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

### 3.3 Clinical Pharmacology Review Questions

*3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?*

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

*3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

*3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?*

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

### 3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

In a dose optimization study (ASCEND-8) in patients receiving ceritinib capsules 450 mg or 600 mg daily with food (approximately 100 to 500 calories and 1.5 to 15 grams of fat) or 750 mg daily under fasted conditions, there was no clinically meaningful difference in the systemic steady-state exposure of ceritinib (AUC) for the 450 mg with food arm compared to the 750 mg fasted arm. The steady-state AUC increased by 24% and C<sub>max</sub> increased by 25% in the 600 mg with food arm compared to the 750 mg fasted arm.

Based on the above study results, the recommended dosage of ceritinib changed from 750 mg orally once daily on an empty stomach to 450 mg orally once daily with food.

### 3.3.5 Is the proposed tablet formulation bioequivalent (BE) to the approved capsule formulation?

Yes, the bioequivalence (BE) of the tablet formulation to the approved capsule formulation is demonstrated by the results of three bioavailability/bioequivalence studies included in this NDA.

#### BE study under fasted conditions

Study LDK378A2107 is a randomized, open-label, single center, two-cohort, two-period, two-sequence crossover study to assess BE of the FCT (150 mg and 375 mg dosage strengths) and HGC (150 mg dosage strength) following single-dose administration of ceritinib at 750 mg under fasted conditions (N = 160, 80/cohort). As seen in Table 1, the 90% confidence intervals (CI) for the primary PK parameters (C<sub>max</sub>, AUC<sub>last</sub>, and AUC<sub>inf</sub>) are all within the BE boundary of 0.80 and 1.25. The geometric mean ratios (GMR) of C<sub>max</sub>, AUC<sub>last</sub>, and AUC<sub>inf</sub> are around 1. The median of T<sub>max</sub> between the tablet and capsule is the same. BE is established between the marketed HGC and test FCT (both at 150 mg and 375 mg dosage strengths) after single-dose administration of ceritinib at 750 mg under fasted conditions. The reported PK parameter values are consistent with FDA's analysis.

Table 1. Summary of statistical analysis of primary PK parameters for ceritinib in Study LDK378A2107

Test/ Reference	Cohort 1 2 × 375 mg tablets (test) vs. 5 × 150 mg capsules (reference)		Cohort 2 5 × 150 mg tablets (test) vs. 5 × 150 mg capsules (reference)	
	Geo-mean ratio by sponsor (90% CI)	Geo-mean ratio by FDA	Geo-mean ratio by sponsor (90% CI)	Geo-mean ratio by FDA
R_AUC <sub>inf</sub>	0.98 (0.87, 1.09)	0.96	0.99 (0.90, 1.10)	0.96
R_AUC <sub>last</sub>	0.97 (0.87, 1.08)	0.97	0.99 (0.89, 1.10)	1.00
R_C <sub>max</sub>	0.96 (0.86, 1.07)	0.97	0.96 (0.87, 1.06)	1.00
Δ_T <sub>max</sub> *	0 (-14.0, 38.0)	0	0 (-6.00, 4.03)	0

\*For T<sub>max</sub>, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.

Adapted from Table 11-4 and 11-6 in Applicant's LDK378A2107 CSR

#### BE Study under fed condition

Study LDK378A2122 is a randomized, open-label, single center, two-cohort, two-period, two-sequence crossover study to assess BE between the FCT (150 mg and 300 mg dosage strength) and HGC (150 mg dosage strength) following single-dose administration of ceritinib at 450 mg or 600 mg under fed conditions with a low-fat low-calorie meal (containing approximately 330 calories and 9 grams of fat) (N = 160, 80/ cohort). As seen in Table 2, the 90% CI for the primary PK parameters (Cmax, AUClast, and AUCinf) are all within the BE boundary of 0.80 and 1.25. The GMRs of Cmax, AUClast, and AUCinf are around 1. The median of Tmax between the tablet and capsule are the same. BE is established between the marketed HGC and test FCT (both at 150 mg and 300 mg dosage strengths) after single-dose administration of ceritinib at 450 and 600 mg under fed condition following a low-fat low-calorie meal. The reported PK parameter values are consistent with FDA's analysis.

Table 2. Summary of statistical analysis of primary PK parameters for ceritinib in Study LDK378A2122

Test/ Reference	Cohort 1 3 × 150 mg FCT (test) vs. 3 × 150 mg HGC (reference)		Cohort 2 2 × 300 mg FCT (test) vs. 4 × 150 mg HGC (reference)	
	Geo-mean ratio by sponsor (90% CI)	Geo-mean ratio by FDA	Geo-mean ratio by sponsor (90% CI)	Geo-mean ratio by FDA
R_AUC <sub>inf</sub>	0.97 (0.93, 1.00)	0.95	0.93 (0.89, 0.96)	0.95
R_AUC <sub>last</sub>	0.97 (0.93, 1.00)	0.93	0.93 (0.90, 0.96)	0.93
R_C <sub>max</sub>	0.99 (0.95, 1.03)	0.92	0.95 (0.92, 0.98)	0.93
Δ_T <sub>max</sub> *	0 (-6.00, 7.98)	0	0 (-9.00, 4.00)	0

\*For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.

Adapted from Table 11-4 and 11-6 in Applicant's LDK378A2122 CSR

### Food effect study

Study LDK378A2121 was a randomized, open-label, single center, three-period, six-sequence crossover study to compare the bioavailability of ceritinib FCT (375 mg dosage strength) following a 750 mg single dose when ceritinib is administered with either a low-fat, low-calorie meal (containing approximately 330 calories and 9 grams of fat) or high-fat, high-calorie meal (containing approximately 1000 calories and 58 grams of fat) vs. the fasted conditions (N = 24). As seen in Table 3, a high-fat meal increased ceritinib AUCinf by 64% and Cmax by 58% and a low-fat meal increased ceritinib AUCinf by 39% and Cmax by 42% as compared with the fasted conditions. The reported PK parameter values are consistent with FDA's analysis. The food effect from Study LDK378A2121 appears to be numerically lower compared to the results of the food effect with a single 500 mg ceritinib capsule dose, which reported that high-fat meal increased ceritinib AUC by 73% and Cmax by 41%, and a low-fat meal increased ceritinib AUC by 58% and Cmax by 43% as compared with the fasted conditions.

Table 3. Summary of statistical analysis of primary PK parameters for ceritinib in Study LDK378A2121

Test/ Reference	Low-fat low-calorie meal (test) vs. fasted condition (reference)		High-fat high-calorie meal (test) vs. fasted condition (reference)	
	Geo-mean ratio by sponsor (90% CI)	Geo-mean ratio by FDA	Geo-mean ratio by sponsor (90% CI)	Geo-mean ratio by FDA
R_AUCinf	1.39 (1.24, 1.57)	1.41	1.64 (1.45, 1.85)	1.61

R_AUClast	1.39 (1.23, 1.56)	1.39	1.62 (1.44, 1.83)	1.65
R_Cmax	1.42 (1.26, 1.60)	1.40	1.58 (1.40, 1.79)	1.66
$\Delta$ _Tmax*	0 (-6.00, 2.00)	0	0 (-4.00, 4.00)	0

\*For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.

Adapted from Table 11-3 in Applicant's LDK378A2121 CSR

### 3.4 Summary of Bioanalytical Method Validation and Performance

The Office of Clinical Pharmacology review team has assessed the adequacy of the following bioanalytical methods used in clinical studies and found them acceptable.

For studies CLDK378A2107, CLDK378A2121 and Study CLDK378A2122, plasma ceritinib (LDK378) concentrations were determined with a validated LC-MS/MS method (b) (4). The table below describes the cross-validation performance.

<b>Cross-validation review summary</b>	No major issue. Method was sufficiently validated to support PK studies with adequate dynamic range.	
<b>Changes in method</b>	N/A	
<b>New validated assay range if any</b>	1.00 ng/mL (LLOQ) to 500 ng/mL for LDK378 using 100 $\mu$ L of human plasma.	
<b>Validation parameters</b>	<b>Cross-validation performance</b>	<b>Acceptability</b>
<b>Calibration curve performance during accuracy &amp; precision</b>	(b) (4)	Yes.
		Yes.
<b>QCs performance during accuracy &amp; precision</b>	(b) (4)	Yes.
		Yes.
		Yes.
<b>Cross-validation</b>	(b) (4)	Yes
<b>List other parameters</b>		N/A

Method performance in study CLDK378A2107		
<b>Assay passing rate</b>	(b) (4)	Yes.

<b>Standard curve performance</b>	(b) (4)	Yes.
<b>QC performance</b>	(b) (4)	Yes,
<b>Method reproducibility</b>	(b) (4)	Yes.
<b>Study sample analysis/ stability</b>	Analyzed within 4.5 months from collection (within established stability from (b) (4))	
<b>Method performance in study CLDK378A2121</b>		
<b>Assay passing rate</b>	(b) (4)	Yes.
<b>Standard curve performance</b>	(b) (4)	Yes.
<b>QC performance</b>	(b) (4)	Yes.
<b>Method reproducibility</b>	(b) (4)	Yes.
<b>Study sample analysis/ stability</b>	Analyzed within 4.5 months from collection (within established stability from (b) (4))	
<b>Method performance in study CLDK378A2122</b>		
<b>Assay passing rate</b>	(b) (4)	Yes.
<b>Standard curve performance</b>	(b) (4)	Yes.
<b>QC performance</b>	(b) (4)	Yes.
<b>Method reproducibility</b>	(b) (4)	Yes.
<b>Study sample analysis/ stability</b>	Analyzed within 4.5 months from collection (within established stability from (b) (4))	

### 3.5 Clinical PK and/or PD Assessments

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

### 3.6 Population PK and/or PD Analyses

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

### 3.7 Exposure-Response Analyses

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

### 3.8 Enrichment, Stratification, and/or Biomarker-based Assessment

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

### 3.9 Mechanistic Safety Assessment

Refer to ceritinib label, as ceritinib is an approved drug, and this NDA is for a new tablet dosage form.

Signatures:

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Xiling Jiang, Ph.D.  
Reviewer  
Division of Clinical Pharmacology V

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Hong Zhao, Ph.D.  
Team Leader  
Division of Clinical Pharmacology V

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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XILING JIANG  
02/01/2019 01:49:08 PM  
No action needed.

HONG ZHAO  
02/01/2019 02:16:15 PM  
I concur.