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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 205755
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	December 24, 2013
PDUFA Goal Date	August 24, 2014
Proprietary Name / Established (USAN) names	Zykadia (Ceritinib, LDK378)
Dosage forms / Strength	Capsules, 150 mg
Proposed Indication(s).	For the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) with an anaplastic lymphoma kinase (ALK) inhibitor
Recommended:	Accelerated Approval

Discipline and Consultants	Primary/Secondary Reviewer
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1. Introduction

On December 24, 2013, Novartis Pharmaceuticals submitted part 3 of New Drug Application (NDA) 205755 to complete a rolling submission. The Applicant proposed the following indication: for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) with an anaplastic lymphoma kinase (ALK) inhibitor.

Ceritinib is a new molecular entity (NME) oral ATP-competitive tyrosine kinase inhibitor of ALK with the drug development goal to overcome intrinsic and acquired mechanisms of resistance to the first generation ALK-inhibitor crizotinib (Xalkori, Pfizer).

The primary trial supporting this NDA are results from CLDK378X2101 (referred to as X2101), an open-label, single arm expansion cohort of a phase 1 dose-escalation trial of ceritinib. The primary efficacy population is comprised of 163 patients with ALK-positive metastatic NSCLC (mNSCLC) who progressed on or were intolerant to crizotinib and received ceritinib 750 mg once daily in the fasted state. Randomized trials of ceritinib in ALK-positive NSCLC are in progress.

2. Background

Lung cancer is the leading cause of cancer death in the U.S., with more people dying of lung cancer than of colon, breast, and prostate cancers combined. Estimated new lung cancer cases for 2014 are 224,210 contributing to 159,260 deaths. NSCLC accounts for approximately 85% of lung cancer cases, with an expected 5-year survival of 1-5% for advanced disease. In unselected patients, cytotoxic platinum doublet-based chemotherapy has historically been the backbone of first-line treatment for patients with metastatic disease, with median survival of approximately 10 to 12 months. In the second-line treatment setting of unselected patients with advanced NSCLC, docetaxel, pemetrexed (non-squamous), and erlotinib are FDA-approved. However, response rates are less than 10%.

In 2007, rearrangements in ALK were identified as oncogenic drivers in nonclinical models and were found in a subset of archived patient lung cancer specimens. ALK is a receptor tyrosine kinase involved in oncogenesis of several cancers due to translocation of the kinase domain with multiple fusion partners resulting in ligand-independent constitutive activation. Within NSCLC, ALK rearrangements (herein referred to as ALK-positive) are detected in about 5% of patients overall, but are more common in younger patients, never-smokers, and patients with adenocarcinoma histology.

In August 2011, FDA approved crizotinib (under accelerated approval) for patients with ALK-positive mNSCLC based on the results of two single arm studies of 255 ALK-positive mNSCLC patients with overall response rates (ORR) of 50 and 61%, corresponding to a median duration of response (DOR) of 9.7 and 11 months, respectively. Crizotinib received regular approval in November 2013 based on a randomized trial (n=347) that demonstrated superior progression-free survival (PFS) for crizotinib-treated patients compared to chemotherapy (pemetrexed or docetaxel) in patients with ALK-positive mNSCLC with disease progression after platinum-based doublet chemotherapy (PFS HR 0.49, median 7.7 versus 3.0 months, p<0.001). ORR was 65% for crizotinib (median DOR 7.4 months) versus 20% (median DOR 5.6 months) for chemotherapy. In an interim Overall Survival (OS) analysis, no difference was observed (HR 1.02, median OS 20.3 versus 22.8 months, p=0.54), however 64% of patients chemotherapy-treated patients received crizotinib after progression.

Nearly all patients with ALK-positive mNSCLC ultimately develop progressive disease on crizotinib, frequently with new brain metastasis. Approximately one third of patients with ALK-positive NSCLC progress due to acquired mutations within the ALK tyrosine kinase domain or amplification of the ALK fusion gene. In the remaining cases, the ALK tyrosine kinase domain and gene are unchanged, and resistance occurs through alternate pathways. Once patients progress on crizotinib, options are limited to chemotherapy or supportive care.

3. CMC

Drug substance and drug product

The Chemistry review team recommends an overall acceptability regarding the manufacturing of the drug product and drug substance.

The drug product is an immediate release hard gelatin capsule for oral administration. The drug product contains ceritinib 150 mg formulated using excipients meeting pharmacopoeia quality standards. Based on the current available stability data, 18 months shelf-life for ceritinib 150 mg hard gelatin capsule stored at 25 degree C (77 degree F) in tight containers is granted.

The Office of Compliance (OC) issued an overall acceptable recommendation on March 27, 2014 for manufacturing and testing facility inspections for the drug substance and drug product. However, the OC had cGMP concerns with the (b) (4) facility, which manufactures the (b) (4) for the ceritinib API. On April 29, 2014, OHOP met with the OC. The OC provided an update on the inspection for the (b) (4) facility and deemed the facility acceptable in terms of manufacture of the API (b) (4)

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical findings that would preclude the approval of ceritinib for the proposed indication.

The major target organs identified in general toxicology studies conducted in rats and monkeys included the pancreas, biliopancreatic ducts, bile duct, gastrointestinal tract and liver. The lungs were also identified as a target organ in rats with phospholipidosis observed following 4 weeks of dosing at 1.5-fold clinical exposure, and lung macrophage aggregates following 13 weeks of dosing at similar exposures to that observed clinically. In animals, high levels of ceritinib were present in the pancreas, and pancreatic atrophy was observed in monkeys and in rats at doses resulting in exposures 0.15 and 1.5-fold the ceritinib exposure at the recommended dose. Effects on the biliopancreatic and bile ducts were observed in animals at exposures lower than the clinical exposure of ceritinib. Hyperglycemia may be related to pancreatic effects of the drug or to inhibition of IGF-1R and InsR.

In a CNS safety pharmacology study, no significant behavioral or physiological changes were observed following a dose of ceritinib. The drug does cross the blood brain barrier. In rats, exposure of ceritinib in the brain was approximately 15% that of the plasma exposure by AUC.

Ceritinib demonstrated potential for causing QTc prolongation in the *in vitro* hERG assay as well as *in vivo* in a single dose cardiac safety pharmacology study conducted in monkeys.

Carcinogenicity

Ceritinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay but was aneugenic in both the *in vitro* cytogenetic assay using human lymphocytes and in micronuclei in the *in vitro* micronucleus test using TK6 cells. Ceritinib was not clastogenic in the *in vivo* mouse micronucleus assay. Seven process impurities were assayed by (b) (4) screening and predicted to be genotoxic, but were controlled to acceptable levels for a drug intended for the treatment of patients with cancer.

Reproductive toxicology

Administration of ceritinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses resulting in maternal exposures less than 50% the human exposure by AUC at the recommended dose. Findings included delayed ossification and skeletal variations. Ceritinib did not induce embryolethality or fetotoxicity at doses tested in rats. In pregnant rabbits administered ceritinib daily during

organogenesis, dose-related skeletal and visceral anomalies, including incomplete ossification, absent or malpositioned gallbladder and retroesophageal subclavian cardiac artery were observed at exposures of approximately 13% of the recommended human exposure by AUC. Higher doses resulted in significant maternal toxicity and abortion in rabbits. In addition, ALK inhibition has been reported to be associated with fetal toxicities including effects on neural development. Therefore, the nonclinical discipline recommended pregnancy category D. Given the 41 hour half-life of ceritinib at the recommended clinical dose, females are advised to use effective contraception during treatment and for up to 2 weeks following cessation of treatment.

5. Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval; however, postmarketing trials will be required.

Following ceritinib 750 mg daily, steady state is achieved by approximately 15 days with 6-fold accumulation after three weeks. The terminal half-life ($t_{1/2}$) at the 750 mg dose is 41 hours. The median ceritinib T_{max} ranged from 4 to 6 hours. The mean accumulation ratio for AUC_{0-24h} is 4.7 (day 8/day 1 of cycle 1) and 6.2 (day 1 of cycle 2/cycle 1).

The ADME in 6 healthy subjects who received a single dose of 750 mg ceritinib suggests the major route of elimination as hepatic. The mean recovery of the administered dose was 92% (68% as unchanged parent compound) in the feces and 1.3% in the urine.

Intrinsic factors: No formal studies have been conducted to assess the effect of age, race, weight, height, or organ dysfunction of exposure and response to ceritinib. The Applicant's population PK (popPK) analysis did not identify clinically important effects of body weight, age gender, mild and moderate renal impairment, and mild hepatic impairment as covariates on clearance or volume of distribution of ceritinib.

- *Hepatic impairment:* Based on a popPK analysis of 48 patients with mild hepatic impairment and 254 patients with normal hepatic function, ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function. The PK of ceritinib has not been studied in patients with moderate to severe hepatic impairment.
- *Renal impairment:* Based on a popPK analysis of 97 patients with mild renal impairment, 22 patients with moderate renal impairment and 183 patients with normal renal function, ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function. Patients with severe renal impairment were not included in the clinical trial.

Extrinsic factors: Ceritinib is primarily metabolized by CYP3A and is a reversible and time- dependent inhibitor of CYP3A and an inhibitor of CYP2C9 *in vitro*; PMRs have been imposed to further evaluate drug interactions between ceritinib and CYP3A and CYP2C9 substrates.

Gastric acid reducing agents may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH- dependent solubility and becomes poorly soluble as pH increases *in vitro*. The sponsor is required to conduct a clinical trial to further investigate the concomitant use of gastric acid reducing agents and ceritinib.

Exposure-Response

Based on currently available data, the proposed dose of 750 mg daily is acceptable. The results of E-R analyses for efficacy did not show a clear relationship between systemic exposure and ORR or PFS. Higher systemic exposure is associated with more frequent and earlier overall Grade 3-4 AEs and higher incidence of individual AEs (Grade 3-4 AST/ALT elevations and Grade 2 or worse hyperglycemia). Higher systemic exposure is also associated with earlier and more frequent dose reductions or dose interruptions. Given that permanent

discontinuations due to AEs occurred in only 10% of patients, the proposed dose of 750 mg with management of AEs via dose reductions or interruptions appears acceptable.

QT assessment

Ceritinib prolonged the QTc interval in a concentration-dependent manner. Following repeat daily doses of 750 mg ceritinib, large changes (i.e., >20 ms) in the QT interval were detected at steady-state. The largest mean change from baseline was 19.3 ms with the upper bound of the 2-sided 90% confidence interval of 22.2 ms, observed at cycle 6 Day 1.

Unresolved Dosing Issue with Regard to gastrointestinal (GI) tolerability

The proposed dosing regimen for ceritinib with regard to food is 750 mg daily on an empty stomach at least 2 hours before or 2 hours after food. At the recommended dose under fasted conditions, the majority of patients experienced GI adverse reactions including diarrhea (86%), nausea (80%), vomiting (60%), and abdominal pain (54%). The food effect study showed that a high-fat, high calorie meal increased ceritinib AUC by 73% and Cmax by 41%; a low-fat meal increased AUC by 58% and Cmax by 43% as compared to fasted conditions.

There are several concerns regarding dosing of ceritinib in patients with hepatic impairment, taking food to alleviate gastrointestinal toxicity, or taking pH-lowering agents, as well as issues regarding the effects of ceritinib on CYP3A4 and CYP2C9 substrates. These issues can be addressed through post-marketing requirements (see action letter), given the agreed-upon statements in product labeling regarding limitations of knowledge in these areas.

6. Clinical/Statistical-Efficacy

The primary trial supporting this NDA are based on the results of a multicenter, single-arm, open-label clinical trial enrolling a total of 163 patients with metastatic, ALK-positive, NSCLC who had progressed on or were intolerant to crizotinib. All patients received ceritinib at a dose of 750 mg once daily.

The primary endpoint supporting approval was ORR according to RECIST v1.0 as evaluated by both investigator and a Blinded Independent Central Review Committee (BIRC). Duration of response (DOR) was also assessed.

The median age of patients was 52 years. The majority of patients were female (54%), and White (66%), never or former smoker (97%), had ECOG Performance Status 0 or 1 (87%) and adenocarcinoma histology (93%). Nearly all patients (91%) had disease progression on previous crizotinib and 84% had received two or more prior therapies for metastatic disease. Sites of extra-thoracic metastasis included brain (60%), liver (42%), and bone (42%).

The trial results demonstrated durable responses of large magnitude with an ORR of 44% (95% CI: 36, 52) and DOR of 7.1 months based on BIRC-determined tumor assessments. The analysis by investigator assessment showed similar results with an ORR of 55% (95% CI: 47, 62) and DOR of 7.4 months. Efficacy data for the FAS by investigator and BIRC is presented in Table 1.

Table 1: ORR and DOR in patients with ALK+ NSCLC who previously received crizotinib (Data cut-off: October 31, 2013)

Efficacy Parameter	Investigator Assessment (N=163)	BIRC Assessment (N=163)
ORR (95% CI)	54.6% (47, 62)	43.6% (36, 52)
CR	1.2%	2.5%
PR	53.4%	41.1%
DOR, median (months) (95% CI)	7.4 (5.4, 10.1)	7.1 (5.6, NE)

CR, complete response; NE, not estimable; PR, partial response.

7. Safety

The safety evaluation of ceritinib was based on 255 patients with ALK-positive tumors (246 patients with NSCLC and 9 patients with other cancers) who received ceritinib at a dose of 750 mg once daily. The most common adverse reactions (greater than or equal to 25%) were diarrhea, nausea, transaminitis, vomiting, abdominal pain, fatigue, decreased appetite and constipation. The most common CTCAE Grade 3-4 adverse reactions (greater than or equal to 5%) were diarrhea, fatigue, transaminitis, hyperglycemia, hypophosphatemia, increased lipase levels, and anemia. Additional serious adverse reactions include interstitial lung disease and QT prolongation.

8. Advisory Committee Meeting

This NDA was not presented to the Oncologic Drugs Advisory Committee (ODAC) because the application did not raise significant or controversial efficacy or safety issues. Two Special Government Employees (SGEs, one physician and one patient lung cancer survivor) were consulted. Both SGEs were concerned about the gastrointestinal toxicity of the drug, but felt that the response rates and duration of response were clinically meaningful.

9. Pediatrics

Ceritinib was granted Orphan Drug Designation for the treatment of patients with ALK-positive NSCLC and is therefore exempt from PREA requirements.

10. Labeling

Proprietary name: OSE/DMEPA concluded that the proposed proprietary name, Zykadia is acceptable.

Prescribing Information: DMEPA, the patient labeling team and OPDP reviewed labeling for this application and their review comments were addressed during the course of team labeling meetings.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Accelerated Approval
- Risk Benefit Assessment

The basis of this approval is the demonstration of a large magnitude of ORR (44% by BIRC, 55% by investigator) of long duration (median of roughly 7 months) in a patient population (ALK-positive mNSCLC refractory to crizotinib) where limited treatment options exist in a serious and life-threatening disease. Response rate of large magnitude and long duration have been observed in trials with other TKIs targeting specific genetic aberrations in mNSCLC, which have subsequently in randomized confirmatory trials demonstrated improvements in PFS of large magnitude when compared to chemotherapy.

As a condition of accelerated approval, the Applicant is required to perform a randomized, multicenter post marketing study (or studies) to confirm the superiority of ceritinib over standard therapy in ALK-positive mNSCLC.

The main risks, as highlighted in the 'Warnings and Precautions' section of the prescriber information, include severe and persistent gastrointestinal (GI) toxicity, hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, hyperglycemia, bradycardia, and embryofetal toxicity.

The dose and schedule of 750 mg daily in the fasted state used in study X2101 is acceptable. However, there remains some concern and uncertainty regarding the severe and persistent gastrointestinal toxicity associated with this dosing. Therefore, the Applicant will conduct a postmarketing study to investigate the safety and exposure of ceritinib 450 mg and 600 mg taken with meals compared to 750 mg taken in the fasted state.

The risk-benefit profile was deemed favorable by Drs. Keegan, Blumenthal and Khozin and I concur with their assessment. Furthermore, all review team members recommend approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
None.
- Recommendation for other Postmarketing Requirements and Commitments
See action letter.

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/s/

RICHARD PAZDUR
04/29/2014