

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205755Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: March 25, 2014

Reviewer(s): Naomi Redd, Pharm.D.  
Division of Risk Management

Team Leader: Cynthia LaCivita, Pharm.D.  
Division of Risk Management

Division Director: Claudia Manzo, Pharm.D.  
Division of Risk Management

Subject: Review to determine if a REMS is necessary

Drug Name(s): ceritinib (Zykadia)

Therapeutic Class: Anaplastic Lymphoma Kinase (ALK) Inhibitor

Dosage and Route: 150 mg capsules, 750 mg by mouth once daily

Application Type/Number: NDA 205755

Applicant/sponsor: Novartis

OSE RCM #: 2013-2768

\*\*\* This document contains proprietary and confidential information that should not be released to the public. \*\*\*

# CONTENTS

1	INTRODUCTION .....	1
1.1	Background .....	1
1.2	Regulatory History .....	2
	MATERIALS REVIEWED.....	2
2.1	Data and Information sources .....	2
3	RESULTS of REVIEW .....	2,3
3.1	Overview of Clinical Program .....	3
3.2	Safety Concerns.....	3
4	PROPOSED POST MARKETING REQUIREMENTS/COMMITMENTS .....	5
5	DISCUSSION.....	5
6	CONCLUSION.....	7

## 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) ceritinib, LDK378. Novartis submitted a New Drug Application (NDA) 205755 for ceritinib with the proposed indication for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

The sponsor was granted breakthrough therapy designation on March 3, 2013, and orphan drug designation status on September 27, 2013. On November 27, 2013 this application was submitted as a 3 part rolling submission, with final submission submitted on December 24, 2013.

The submission did not include a REMS but included a Risk Management Plan which was comprised of labeling and routine pharmacovigilance. The Division of Pharmacovigilance will provide comments on the proposed the pharmacovigilance plan in a separate review.

### 1.1 BACKGROUND

Lung cancer is the most common cause of cancer related deaths worldwide. The American Cancer Society estimates 224,210 new cases of lung cancer will be diagnosed in the United States, with an estimated 159,260 lung cancer related deaths in 2014.<sup>1</sup> NSCLC accounts for nearly 85% of lung cancers, and results in more cancer related deaths worldwide than any other malignancy. Patients with NSCLC generally present at diagnosis with locally advanced or metastatic disease, with poor prognosis and median survival rates of less than one year.<sup>2</sup>

Recent developments in the molecular biology of lung cancer have resulted in the identification of specific, targetable oncogenic driver mutations in a subset of NSCLC, several of which have been the basis for targeted pharmacotherapy for this patient population. ALK is a key oncogenic driver mutation that has recently been discovered in NSCLC. This re-arrangement often occurs with fusion of other oncogenic proteins on receptors of the tyrosine kinase domain.<sup>3</sup> Demographics show a higher prevalence in light smokers ( $\leq 10$  pack year smokers), never smokers, females, and younger patients often less than 60 years of age.<sup>4</sup>

ALK re-arrangement is a rare event; reported in 2-5% of the NSCLC population, which translates to approximately 70,000 patients globally each year, and approximately 10,000 patients in the United States.<sup>1</sup> Although there have been improvements in chemotherapy administration and development of new cytotoxic agents over the last 10 years, this has

---

<sup>1</sup>American Cancer Society Lung Cancer Statistics. [www.cancer.org/cancer/lungcancer-nonsmallcell/detailedguide/non-small-cell-lung-cancer-key-stastics](http://www.cancer.org/cancer/lungcancer-nonsmallcell/detailedguide/non-small-cell-lung-cancer-key-stastics) accessed March 13th, 2014.

<sup>2</sup> Mologni L. Inhibitors of the anaplastic lymphoma kinase. *Expert Opinion Investig. Drugs.*; 2012; 21(7) 985-994

<sup>3</sup>Gridelli C et al. ALK inhibitors in the treatment of advanced NSCLC. *Cancer Treatment Reviews.* May 2013; 300-306.

led to marginal improvements in 5 year survival rates from 15.7% to 17.5%.<sup>4</sup> Crizotinib (Xalkori®) is currently the only FDA approved oral agent for treatment of ALK-positive NSCLC, however acquired resistance has been reported in approximately 28% of patients progressing on crizotinib within 1-2 years of therapy.<sup>5</sup> After patients have failed crizotinib therapy, there are no other options to treat their disease.

Ceritinib is an orally-active, small molecule, ATP-competitive inhibitor of ALK kinase.<sup>6</sup> This molecule inhibits auto phosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both in vivo and in vitro.<sup>6</sup> Activity against ALK-positive tumors expressing the gatekeeper mutation C1156Y, insulin growth factor 1, as well as crizotinib resistant strains have been demonstrated in preclinical trials.<sup>5</sup> Novartis is seeking approval for NME ceritinib 750mg daily for the treatment of (b) (4) metastatic NSCLC who have

## 1.2 REGULATORY HISTORY

- March 6<sup>th</sup>, 2013: Ceritinib granted Breakthrough Therapy designation for the treatment of patients with metastatic NSCLC that is ALK-positive as detected by an FDA approved test and which has progressed during treatment with crizotinib or where patients are intolerant to crizotinib.
- September 27<sup>th</sup>, 2013: Orphan drug designation granted.
- November 22, 2013: Pre-NDA meeting where rolling submission was granted and proposed timelines submitted by the applicant were agreed upon by FDA.
- November 27, 2013: Part 1 of rolling submission.
- December 12, 2013: Part 2 of rolling submission.
- December 24, 2013: Part 3 of rolling submission.

## 2 MATERIALS REVIEWED

### 2.1 DATA AND INFORMATION SOURCES

- LDK378 Clinical Overview, Novartis – section 2.5
- LDK378 Clinical Safety Summary, Novartis – section 2.7.4
- LDK378 Core Safety Risk Management Plan, Novartis
- FDA Application Orientation meeting, January 31, 2014
- Midcycle presentation slides, NDA 205755, February 25<sup>th</sup>, 2014

## 3 RESULTS OF REVIEW

### 3.1 OVERVIEW OF CLINICAL PROGRAM

---

<sup>4</sup> Alamgeer M et al. Novel therapeutic targets in non-small cell lung cancer. *Current Opinion in Pharmacology* 2013, 13:394-401

<sup>5</sup> FDA Application Orientation Meeting, ceritinib, 31 January 2014

<sup>6</sup> Ceritinib Clinical Overview, Section 2.5, Novartis

Registration study LDK378X2101 (also referred to as study X2101) was the first-in-human study to assess the effectiveness of ceritinib in ALK positive NSCLC patients. This is multicenter, single-arm, open-label, dose escalation study that enrolled 304 ALK-inhibitor experienced and ALK-inhibitor naïve patients. The study was extended to include an expansion phase to characterize the efficacy, safety, and pharmacokinetics of ceritinib. The maximum tolerated dose (MTD) and recommended dose (RD) evaluated doses from 50 mg to 750 mg daily in 59 patients. An additional 245 patients were included in the expansion phase, with the primary endpoint of overall response rate (ORR) per RECIST 1.0 criteria.<sup>6</sup>

Of the 304 patients included in study X2101, 290 were confirmed to have ALK positive NSCLC by FISH (Fluorescent in Situ Hybridization), and 246 received the RD of 750 mg daily. Of the 246 patients that received the RD of ceritinib, 83 were ALK-inhibitor naïve, and 163 patients were ALK-inhibitor experienced.<sup>6</sup> Since the applicant is seeking an indication for experienced patients, the 163 ALK-inhibitor experienced patients were evaluated for the safety analysis for this trial.

Patient demographics were consistent with characteristics of ALK-positive NSCLC patients. Median age was 53 years, and 98% had never smoked or were ex-smokers. All patients had locally advanced or metastatic disease, with over 50% of patients with brain metastases, and nearly 40% with liver metastases. The patients in this study were heavily pretreated with multiple antineoplastic regimens; 67.5% having prior treatment with at least 2 regimens. All of the ALK-inhibitor experienced patients were previously treated with crizotinib, with disease progression in 91.4% of these patients when they entered ceritinib trials.

**Key Efficacy Findings:** The primary efficacy analysis was evaluated based on data from the 246 patients who had received the RD of ceritinib. One hundred and eighty patients received ceritinib at least 18 weeks prior to the data cut-off date and were included in the efficacy analysis. This analysis also included ALK-inhibitor naïve patients.

Overall, 60% of these patients achieved the primary endpoint of ORR per RECIST 1.0 criteria: 69.5% of ALK-inhibitor naïve patients, and 55.4% of ALK-inhibitor experienced patients. A secondary endpoint of duration of response (DOR) was also assessed, and reported to be approximately 8 months in ALK-inhibitor experienced patients. Another secondary endpoint, Progression-free survival (PFS) was approximately 7 months, with an estimated 6 month and 12 month progression-free survival rate of 54% and 25% respectively.

## 3.2 SAFETY CONCERNS

Gastrointestinal (GI) toxicity was noted in 98% of patients, which was managed by holding or reducing the dose of ceritinib. Serious adverse events of concern include hepatotoxicity, QT prolongation, pneumonitis and possible pancreatitis.

**3.2.1 Hepatotoxicity** – Increases in transaminase levels were frequently reported with ceritinib treatment, with ALT and/or AST increases greater than 3 times the upper limit of normal in 38.8% of patients at the RD in study X2101. Similarities in the frequency and severity of transaminase increases were similar in 41% of patients receiving the lower dose range of 400-700mg.<sup>6</sup> Laboratory data showed ALT

increases greater than 5 times the upper limit of normal in 27% of patients and increases greater than 20 times the upper limit of normal in 1.3% of patients.<sup>7</sup> Two cases of drug-induced liver injury were reported, however, there were no cases of Hy's law. One patient required permanent discontinuation due to elevated transaminases and jaundice. Fifty-two percent of patients received at least 1 dose reduction due to increases in transaminases. The majority of the dose reductions occurred during the first 12 weeks of treatment in 76% of patients, with the average reduction in dose to 600mg daily.<sup>6</sup> There were no cases of death reported due to hepatic failure.

**3.2.2 QT prolongation** – Ceritinib has inhibitory activity on the hERG potassium channels suggesting that there is a clinical risk for QTc prolongation (QTcP). At steady-state C<sub>max</sub> concentrations, the estimated increase in QTcP from baseline was 13.6ms and at concentrations as high as the 75% percentile of C<sub>max</sub>, the mean QTcP change from baseline was <20ms indicating a moderate risk for QT prolongation.<sup>6</sup> However, 6% of patients had adverse events related to QT prolongation, of which 0.7% (n = 2) that were reported as serious adverse events.<sup>7</sup> One patient had grade 4 cardio-respiratory arrest and died. The other serious case was in a patient who experienced loss of consciousness that was attributed to brain metastases and subsequently died 10 days later. Both of these events were attributed to disease progression. There were 6 patients with grade 3-4 events (3 with electrocardiogram QT prolongation, and syncope in 3 patients); however they were all reported as non-serious. There were no cases of Torsade de Pointes, and no discontinuations from the study due to QT prolongation.<sup>7</sup>

**3.2.3 Interstitial Lung Disease (ILD)/Pneumonitis** – Two fatal cases of pneumonitis were reported; 1 case in study X2101 with the RD of ceritinib, and 1 case in another study (X2102) in the 600mg dose.<sup>5</sup> ILD/pneumonitis was reported overall in 4% of patients, with grade 3-4 adverse events in 3% of patients.<sup>5</sup>

**3.2.4 Other safety topics of interest:**

- **Bradycardia** – Sinus bradycardia and bradycardia were each reported in 1.6% of all patients (all Grade 1).<sup>6</sup> Bradycardia related to ECG QT prolongations was included with QT prolongation events. Mean decrease in heart rate was 8.9 bpm from baseline, but remained normal (72.8 bpm).<sup>6</sup> None of the events were serious or led to study discontinuation.
- **Hyperglycemia** – Adverse events of hyperglycemia were reported overall in 8% of patients, of which grade 3-4 events were reported in 5% of patients. New onset diabetes was reported in 7 patients.<sup>7</sup> One case was suspected to be related to ceritinib, and the other 6 were attributed to corticosteroid therapy treatment for pneumonitis or CNS events. Time to onset of diabetes varied from 11 days to 253 days. Patients who developed hyperglycemia and/or new onset diabetes were

---

<sup>7</sup> LDK378 Core Risk Management Plan, Novartis

treated with anti-diabetic medications, or managed with dose reduction or interruption. There were no discontinuations due to hyperglycemia.

- **Pancreatitis** – In nonclinical data, repeated doses of ceritinib in rats and monkeys up to 13 weeks led to vacuolation, hypertrophy, inflammation, erosion, necrosis, and hyperplasia in the biliary and pancreatic ducts. Approximately 10% of patients exhibited signs and symptoms of acute pancreatitis.<sup>8</sup> Asymptomatic elevations in amylase and lipase were noted as grade 1 or 2 elevations, and managed with dose reductions. These events were filtered by the Sponsor because GI toxicity is reported in nearly all patients in the trial, and therefore may confound true effects of pancreatitis.

**3.2.5 Reproductive toxicity** – Ceritinib is teratogenic at 10 and 50 mg/kg in rabbits and rats, respectively. Dose-related skeletal anomalies were seen in both species. The sponsor has proposed pregnancy category D, and FDA concurs with this category rating.<sup>8</sup>

**3.2.6 Deaths:** Forty deaths were reported on treatment in Study X2101 at all doses, and were defined as deaths that occurred during treatment or within 28 days of the last dose of ceritinib. Two cases of fatal ILD/pneumonitis were reported in ceritinib trials. All other deaths reported were attributed to disease progression.

The applicant plans to address all safety events in labeling, and therefore did not submit a REMS.

#### **4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS**

The following post-marketing requirements/commitments have been proposed:

1. Evaluate the food effect and various doses on ceritinib.
2. Complete a pharmacokinetic trial to determine the appropriate dose of ceritinib in patients with hepatic impairment.
3. Conduct a clinical trial evaluating the effects of repeat doses of ceritinib on the single dose pharmacokinetics of midazolam (CYP3A4 substrate).
4. Conduct a clinical trial evaluating the effects of repeat doses of ceritinib on the single dose pharmacokinetics of diclofenac (CYP2C9 substrate).
5. Conduct a clinical trial to determine how to dose ceritinib with regard to gastric pH elevating agents (e.g., a proton-pump inhibitor, an H<sub>2</sub>-receptor antagonist, and an antacid).

#### **5 DISCUSSION**

Patients diagnosed with ALK-positive NSCLC represent a narrow population of patients who ultimately die as a result of their disease. Despite advances in chemotherapy and targeted molecular pharmacotherapy, survival rates in this patient population are

---

<sup>8</sup> FDA Midcycle Communication Presentation Slides, February 25<sup>th</sup>, 2014

suboptimal. Crizotinib is an oral ALK-inhibitor that received accelerated approval by the FDA in August 2011 for the treatment of patients with ALK-positive NSCLC. Unfortunately, patients invariably develop resistance to this drug within 1-2 years of therapy. Currently there are no other approved treatment options after patients have failed crizotinib.

Ceritinib is a NME that is seeking an indication for the treatment of (b) (4) metastatic NSCLC in (b) (4) patients. The safety and efficacy of ceritinib is based on results of Study X2101, a single-arm, open-label study in which 163 NSCLC patients were heavily pretreated with prior chemotherapy and crizotinib. Fifty-five percent of these patients achieved the primary endpoint of ORR per RECIST 1.0 criteria. Secondary endpoints of DOR and PFS were approximately 8 months and 7 months respectively.

Gastrointestinal toxicity was associated with ceritinib therapy in 98% of patients, and managed by either holding the drug or reducing the dose. The applicant submitted a Risk Management Plan that addresses adverse events of special interest which include: hepatotoxicity, QT prolongation, and pneumonitis. Other safety topics included in the Risk Management Plan include bradycardia and hyperglycemia. Upon review of this application from the clinical team, pancreatitis was also noted to be a possible concern with ceritinib.

The risks associated with ceritinib treatment are similar in crizotinib, as well as other antineoplastic agents in the tyrosine kinase inhibitor class. Major risks associated with ceritinib include hepatotoxicity, ILD/pneumonitis, and QT interval prolongation; and to a lesser extent bradycardia, hyperglycemia, and potentially pancreatitis. Hepatotoxic events for crizotinib are associated to a some-what lesser extent compared to ceritinib. Fatal hepatotoxicity was reported in 2 of 1225 patients treated with crizotinib, 8 patients required permanent discontinuation due to elevated transaminases, and 7 patients (0.6%) had concurrent elevations in ALT greater than 3 times the upper limit of normal.<sup>9</sup> This is lower than the 40% of patients reported for ceritinib. QT interval prolongation has also been reported with crizotinib. Clinical studies reported occurrence in 2.7%<sup>9</sup> of patients which is similar to ceritinib. Other antineoplastic agents such as nilotinib (Tasigna) and vandetanib (Capresla) which also have a risk of QT prolongation, required a REMS due to significant effect that the risks has on the intended patient population. Of note, the REMS for nilotinib was removed in May 2013. As with ceritinib, fatal ILD/pneumonitis has also been reported in crizotinib trials; 6 cases in crizotinib trials<sup>9</sup> and 1 case reported with ceritinib. Overall rates of ILD/pneumonitis rates are similar with both agents with 2.5%<sup>9</sup> in crizotinib patients and 4% in ceritinib patients. Both crizotinib and ceritinib are labeled as pregnancy category D.

At this time, these events will be managed through labeling with ceritinib. Crizotinib was approved in 2011 without a REMS, and all of the above risks are currently managed through labeling in the warnings and precautions section. There are no boxed warnings in the label for either drug.

---

<sup>9</sup> XALKORI (crizotinib) Prescribing Information. Revised November 2013

Ceritinib will be primarily, if not exclusively, prescribed by oncologists who are familiar with the adverse events associated with ceritinib treatment and the management thereof. Furthermore, the efficacy seen in study X2101 provides a therapeutic option for ALK-experienced NSCLC patients who have failed prior therapies.

## **6 CONCLUSION**

Data presented for this application in this ALK-experienced patient population studied with advanced NSCLC, demonstrate that the benefits of ceritinib outweigh the risks at this time. DRISK concurs with the Division of Oncology Products-2, that based on the available data and the potential benefits and risks of treatment, a REMS is not necessary for ceritinib. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit risk profile to be re-evaluated.

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

/s/  
-----

NAOMI B REDD  
03/25/2014

CLAUDIA B MANZO  
03/25/2014  
concur