CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208434Orig1s000

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:	November 6, 2015
Reviewer(s):	Mona Patel, Pharm.D. Division of Risk Management
Acting Team Leader:	Naomi Redd, Pharm.D. Division of Risk Management
Division Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Subject:	Review to determine if a REMS is necessary
Drug Name(s):	Alecensa (alectinib)
Therapeutic Class:	anaplastic lymphoma kinase (ALK) receptor tyrosine kinase inhibitor
Dosage and Route:	600 mg orally twice daily (BID)
Division:	Division of Oncology Products – 2 (DOP-2)
Application Type/Number:	NDA 208434
Applicant/sponsor:	Hoffman-La Roche, Inc.
OSE RCM #:	2015-1396 2015-1399

CONTENTS

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME) Alecensa (alectinib). The applicant, Hoffman-La Roche, submitted a New Drug Application (NDA) 208434 for their proposed indication of treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Hoffman-La Roche submitted a risk management plan with identified risks of interstitial lung disease (ILD)/pneumonitis, bilirubin and hepatic transaminase elevations, photosensitivity, and bradycardia. A potential risk associated with alectinib identified in the risk management plan is embryo-fetal toxicity. Hoffman-La Roche's submission included a pharmacovigilance plan, which included management of these events through routine pharmacovigilance and product labeling. Hoffman-La Roche did not submit a REMS for this application.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Risk Management Plan Module (section 1.16)
- Hoffman-La Roche Clinical Modules (sections 2.5, 2.7.3 and 2.7.4)
- Hoffman-La Roche Clinical Study Reports (section 5)
- Hoffman-La Roche Nonclinical Modules (sections 2.4)
- Midcycle Meeting slides, September 25, 2015
- Alecensa (alectinib) draft label, October 23, 2015

3 REGULATORY HISTORY

The review timeline for this application is Priority. Listed below are the pertinent regulatory history milestones for this NDA:

- September 29, 2011 – IND 111723 submitted for alectinib
- June 5, 2015 – Part 1 of Rolling NDA
- June 19, 2015 – Part 2 of Rolling NDA
- July 6, 2015 – Part 3 of Rolling NDA
- September 25, 2015 – Midcycle meeting
- October 14, 2015 – Midcycle teleconference with the sponsor
- November 6, 2015 – Late-Cycle Meeting
- PDUFA (Action) date – January 1, 2016

4 ASSESSMENT OF NEED FOR A REMS

4.1 RATIONALE FOR DRUG DEVELOPMENT[1]

Lung cancer is the leading cause of cancer related deaths in the Unites States (US), with more people dying of lung cancer than of colon, breast, and prostate cancers combined. In the US, lung cancer represents the second most common type of cancer.[2] According to the American Cancer Society (ACS), an estimated 221, 200 new cases (115, 610 in men and 105, 590 in women) will be diagnosed in 2015 and an estimated 158,040 deaths from lung cancer will occur. Also, according to ACS, lung cancer mainly occurs in older people. About 2 out of 3 people diagnosed with lung cancer are 65 or older, and fewer than 2% of all cases are found in people younger than 45. The average age at the time of diagnosis is about 70. Black men are about 20% more likely to develop lung cancer (including all types) than are white men. The rate is about 10% lower in black women than in white women. In contrast, black men are about 15% *less* likely to develop small cell lung cancer than are white men, and the risk is about 30% lower in black women than in white women.[2]

The two major histological subtypes of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for nearly 85% of all cases of lung cancer, with an expected 5-year survival of 1-5% for advanced disease.[3] Approximately 5% of patients with NSCLC have tumors that contain the ALK-positive chromosomal rearrangement.

Crizotinib is the only currently approved first-line treatment for patients with metastatic NSCLC (mNSCLC) whose tumors are ALK-positive. Unfortunately, nearly all patients with ALK-positive mNSCLC ultimately develop progressive disease on crizotinib, frequently in the Central Nervous System (CNS) with new brain metastasis. Approximately one third of patients with ALK-positive mNSCLC 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.[3] Once patients progress on crizotinib, treatment usually consists of ceritinib, cytotoxic chemotherapy, palliative radiotherapy, and/or supportive care. Ceritinib is the only treatment approved for refractory treatment of ALK-positive mNSCLC for those patients who have progressed on crizotinib. In clinical trials, ceritinib had 43.6% objective response rate (ORR) and a duration of response (DOR) of 7.1 months, but there was sub-optimal control of CNS metastases. was .[4] Therefore, there still is an unmet medical need for ALK-positive mNSCLC patients who have progressed on crizotinib treatment.

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[1] Clinical Overview (section 2.5), alectinib

[2] http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics

[3] Secondary Review of Zykadia (ceritinib) by Gideon Blumenthal April 11, 2014

[4] Zykadia (ceritinib) USPI July 2015

Alectinib is a small molecule ALK receptor tyrosine kinase inhibitor involved in oncogenesis of several cancers due to translocation of the kinase domain with multiple fusion partners resulting in ligand-independent constitutive activation. Alectinib also blocks downstream signaling pathways such as STAT3, P13K/AKT and MAPK. The first approval of alectinib in the world was in Japan on July 4, 2014 and was indicated for the treatment of patients with ALK-positive unresectable, recurrent or advanced NSCLC. The indication for this application was revised by the review division to be indicated for the treatment of patients with ALK-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on crizotinib. The recommended dosing regimen is alectinib 600 mg orally twice daily (BID) until disease progression or unacceptable toxicity. If patients required a dose due to reduction, the first reduction was to a dose of 450 mg orally BID and a second dose reduction to 300 mg orally BID. The drug was to be discontinued if patients were unable to tolerate the 300 mg BID dose. (b) (4)

4.2 CLINICAL DEVELOPMENT PROGRAM

Efficacy data for alectinib for the treatment of patients with ALK-positive, mNSCLC who have progressed on crizotinib were derived from 2 pivotal Phase 1/2 studies submitted to this NDA. These were Study NP28761 and Study NP28673. The development program also included supportive data from Phase 1/2 Study AF-001JP.

4.2.1 Efficacy

At the time of this review, the medical officer's review was ongoing and therefore the final analysis could differ from the sponsor's conclusions. The summary below provides a high level overview of the studies that support this application.

Key Efficacy Findings:[5,6] Please refer to the clinical review by Dr. Erin Larkins for the full review on efficacy and safety. The following is a summary of the key findings from labeling discussions for alectinib as of **October 23, 2015**.

Study NP28761 is an ongoing multi-center, single arm, open-label, dose escalation study to determine the safety, tolerability and activity of alectinib as a single agent in patients with either locally advanced (AJCC Stage IIIB) and not amenable to curative therapy or metastatic (AJCC Stage IV) ALK-positive NSCLC who had experienced disease progression on crizotinib with or without prior chemotherapy. The study was conducted in two parts. The Phase 1 portion was a dose-escalation study to determine the safety of alectinib, the recommended Phase 2 dose (RP2D) of alectinib, and to assess the pharmacokinetics (PK) of alectinib to determine if alectinib should be administered with or without food in Phase 2. The Phase 2 portion of the study evaluated the efficacy, Quality of Life, PK, as well as the safety profile during treatment with alectinib at the RP2D. The results of the Phase I portion of Study NP28761 supported the selection of the 600 mg BID dosing regimen as the RP2D for evaluation of alectinib efficacy and safety in Phase II of Study NP28761 and Study NP28673.

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[5] Alecensa (alectinib) draft label, October 23, 2015

[6] Alecensa (alectinib) Summary of Clinical Efficacy (Section 2.7.3)

For both phases, the primary endpoint was objective response rate (ORR) based on Independent Review Committee (IRC) assessment. ORR was 46% which was considered clinically meaningful as assessed by the FDA clinical reviewer. In the Phase 2 part, the secondary endpoint of ORR, based on investigator assessment, and IRC assessed disease control rate (DCR) was 46% and 79.7% respectively. The CNS objective response rate (CORR) was 68.8% which was considered clinically meaningful. The estimated median Duration of Response (DOR) was 7.5. The other secondary endpoints, progression-free survival (PFS), overall survival (OS), and CNS DOR (CDOR) were immature at the primary data cutoff date.

The baseline demographics and disease characteristics of the study population in Study NP28671 was consistent with that of a mNSCLC ALK-positive population. The median age was 54 years, 55% were females, 73% were white, 35% of patients had an Eastern Cooperative Oncology Group (ECOG) of 0, 55% had an ECOG of 1, and 62% of patients did not have a smoking history. At the time of enrollment for both parts of the study, almost all patients (99%) had Stage IV disease with adenocarcinoma being the predominant histologic subtype [100% (Part 1) and 94% (Part II)].

In this study, patients were enrolled in 26 centers in the US and 1 center in Canada. The first patient was enrolled on May 3, 2012. In the Phase 1 portion of the study, 47 patients were enrolled to receive 240 mg orally (single dose) fasted, 300 (fasted), 460, 600, 760, 900 mg BID under fed conditions. Eighty seven patients were enrolled in the Phase 2 portion of the study to receive 600 mg BID under fed conditions as long as none of the withdrawal criteria (i.e., patient requests discontinuation, disease progression, woman becomes pregnant, or other reason) were met. Each alectinib treatment cycle lasted 21 days.

Study NP28673 is an ongoing Phase 1/2 single arm, open-label, non-randomized, multicenter study to determine the pharmacokinetics, safety, tolerability and activity of alectinib as a single agent in patients with either locally advanced (AJCC Stage IIIB) and not amenable to curative therapy, or metastatic (AJCC Stage IV) ALK-positive NSCLC who have experienced disease progression on crizotinib with or without prior chemotherapy. The study was conducted in three parts: a dose escalation phase, a safety and efficacy evaluation phase, and a post-progression treatment phase.

The primary endpoint was ORR based on IRC assessment. ORR was 44% and was considered clinically meaningful. Secondary endpoints were similar with those of Study NP28671. DCR was 63.9% and CORR was 57.1%. The estimated median DOR was 12 months. The other time-to-event endpoints (CDOR, CPR and OS) were immature at the data cutoff date and required further follow-up.

The baseline demographics and disease characteristics of the study population was consistent with the above study. The median age was 52 years, 56% were females, 67% were white, 32% of patients had an ECOG of 0, 59% of patients had an ECOG of 1, and 70% of patients did not have a smoking history. At the time of enrollment, almost all patients (99%) had Stage IV disease with adenocarcinoma being the predominant histologic subtype (96%).

In this study, patients were enrolled in 56 centers in 16 countries globally. The Phase I (dose escalation phase) portion of Study NP28673 was not completed as the

recommended Phase II dose was already determined in Study NP28761. The first patient was enrolled in the Phase II portion on June 20, 2013. A total of 138 patients were enrolled to receive 600 mg orally BID until disease progression, death, or withdrawal as stated above.

4.2.2 Safety[5,7]

The safety of alectinib is based on analysis of data from 100 patients in Study NP28761 and 153 patients in Study NP28673. The safety data was pooled for Study NP28761 and NP28673. In the Phase 1 portion of Study NP28671, 4% of patients had major protocol violations during the study due to use of prohibited medications. In the Phase 2 portion of the study, 9% of patients had major protocol violations due to use of prohibited medications, missing tumor assessment, or study drug not taken according to protocol.[8] In Study NP28673, 15% of patients had major protocol violations during the study for similar reasons.[9]

The median duration of treatment for alectinib in the Phase 1 and Phase 2 part of Study NP28761 was 58 and 20 weeks respectively and for Study NP28763 was 27 weeks.

The frequency of adverse events (any grade and Grade 3-4) were tabulated using the Medical Dictionary for Regulatory Activities by system organ class and preferred terms using 17.0 for the primary studies and the Roche INN Drug Terms and Procedures Dictionary for treatments. The intensity of adverse events was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Serious adverse reactions (SAEs) occurred in 16% of patients; the most frequently reported serious adverse reaction was pulmonary embolism (1.2%). Fatal adverse reactions occurred in 2% of patients, consisting of hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%), and pulmonary embolism (0.4%). Treatment-related events that were reported in ≥ 10% of patients were fatigue (17%), constipation (16%), myalgia (15%), AST increased (13%), edema peripheral (12%), ALT increased (12%), and blood CPK increased (11%). Twelve (5%) patients experienced SAEs that were considered by the investigator to be treatment related, including one patient who experienced hemorrhage which led to a fatal outcome and another patient who experienced intestinal perforation which led to a fatal outcome.

Dose modifications (interruption or reduction) due to an adverse reaction occurred in 66 patients (26%) in Study NP28671 and NP28673. More patients experienced adverse events leading to dose interruptions (23%) than dose reductions (10%). The most frequent adverse reactions that led to dose reductions or interruptions were elevations in ALT (4%), bilirubin (4%), creatinine phosphokinase (CPK) (4%), AST (3%), and vomiting (3%).

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[7] Alecensa (alectinib) Summary of Safety (Section 2.7.4)

[8] Alecensa (alectinib) Clinical Study Reports Section 5 June 19, 2015 (Study NP28671 Protocol (v.7.0 December 17, 2013)

[9] Alecensa (alectinib) Clinical Study Reports Section 5 June 19, 2015 (Study NP28673 Protocol (v. 5.0 May 2015)

The median time to dose reduction was 28 days, the median time to dose interruption was 42 days, and the median duration of study drug interruption was 7 days. Permanent discontinuation of alectinib for adverse reactions occurred in 5% of patients. The most frequent adverse reactions that led to permanent discontinuation were increased bilirubin (1.6%) and increased ALT levels (0.8%).

This review highlights the alectinib related AEs which were of concern to the review division: hepatotoxicity, ILD, bradycardia, severe myalgia and creatine phosphokinase elevations.

Hepatoxicity: Elevations of AST and ALT greater than 5 times the upper limits of normal (ULN), or bilirubin greater than 3 times the ULN occurred in 3.6%, 4.8%, and 2.8% of patients, respectively. In 76% of the patients with hepatic transaminase elevations and 53% of the patients with bilirubin elevations, these events occurred during the first 2 months of treatment. There was one case of drug-induced liver injury of Grade 3 severity in a patient with prior alcohol history and liver metastases. There were no cases of Hy's Law. The events resolved upon interruption or dose reduction. In 1.2%, 1.6%, and 1.6% of the patients, AST, ALT, and bilirubin elevations, respectively, led to withdrawal from alectinib treatment. If ALT or AST elevation was greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 2 times ULN, then alectinib was be temporarily withheld until recovery to baseline or to less than or equal to 3 times ULN, then resumed at a reduced dose as described above. If ALT or AST elevation was greater than 3 times ULN with total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis, then alectinib was to be permanently discontinued.

Interstitial Lung Disease: Grade 3 ILD occurred in one (0.4%) of 253 patients exposed to alectinib in clinical trials. If any patient presented with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough and fever), alectinib was to be withheld and promptly investigated for ILD. If ILD was confirmed, alectinib was to be permanently discontinued.

Bradycardia: Cases of bradycardia (7.5%) have been reported in patients treated with alectinib. In cases of symptomatic bradycardia, alectinib was to be withheld until recovery to a symptomatic bradycardia or to a heart rate of 60 bpm or above. If a contributing concomitant medication was identified and discontinued, or its dose was adjusted, alectinib was to be resumed at the previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication was identified, or if contributing concomitant medications were not discontinued or dose modified, alectinib was to be resumed at a reduced dose as described above upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. In life-threatening cases, alectinib was to be permanently discontinued if no contributing concomitant medication was identified. If a contributing concomitant medication was identified and discontinued, or its dose adjusted, alectinib was to be resumed at a reduced dose as described above upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above with frequent monitoring as clinically indicated. Alectinib was to be permanently discontinued in cases of recurrence.

Severe Myalgia and Creatine Phosphokinase (CPK) Elevation: Myalgia or musculosketal pain occurred in 29% of patients. The incidence of Grade 3 myalgia/ musculoskeletal pain was 1.2%. Dose modifications for myalgia/musculoskeletal pain were required in 2 of 253 patients (0.8%). Elevations of blood creatine phosphokinase (CPK) occurred in 43% of 218 patients. The incidence of Grade 3 elevations of CPK was 4.6%. Dose modifications for elevation of CPK occurred in 11 of 218 patients (5.0%). If CPK elevation was greater than 5 times ULN, alectinib was to be temporarily withheld until recovery to baseline or to less than or equal to 2.5 times ULN, then resumed at the same dose. If CPK elevation was greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN occurred, alectinib was to be withheld until recovery to baseline or to less than or equal to 2.5 times ULN, then resumed at a reduced dose as described above.

Deaths:[10] A total of 36 patients in the alectinib group died. Of these patients, 31 patients died due to disease progression. For the 5 patients who died due to reasons other than disease progression, patients died of a related adverse event (i.e., hemorrhage (2), intestinal perforation (1), worsening pulmonary embolism (1), and dyspnea (1). Only one of the cases of hemorrhage and intestinal perforation was related to study drug.

Clinical Assessment Based on Pharmacology/Toxicology Findings

Embryo-fetal toxicity:[11] Based on the drug's mechanism of action and findings from animal reproduction studies, alectinib could cause fetal harm when administered to a pregnant woman. Alectinib caused abortion or fetal death in pregnant rabbits and embryo-fetal toxicity in pregnant rats at doses equivalent to 2.7 times the recommended human dose of 600 mg twice-daily. Females of reproductive potential were to use effective contraception during treatment with alectinib and for 1 week following the final dose.

The applicant proposed to communicate all safety events through labeling and therefore did not submit a REMS. The above adverse events will be communicated in labeling under Warnings and Precautions. The fertility and embryo-fetal toxicity was also a concern based on nonclinical safety findings and will be addressed in the Warnings and Precautions section of the labeling.

4.3 ASSESSMENT OF RISK: BENEFIT PROFILE

Despite the availability of ceritinib as a second-line treatment to ALK-positive mNSCLC, there still remains an unmet medical need for ALK-positive mNSCLC patients who have progressed on crizotinib treatment that have a manageable and well tolerated safety profile, especially in CNS activity. Alectinib is indicated for the treatment of patients with ALK-positive, mNSCLC who have progressed on crizotinib.

The anticipated duration of use for alectinib is 600 mg orally BID until disease progression or unacceptable toxicity.

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[10] September 25, 2015 Midcycle Meeting Slides

[11] Alecensa (alectinib) Nonclinical Overview 2.4

Crizotinib is the only currently approved first-line treatment for patients with mNSCLC whose tumors are ALK-positive. Current FDA approved treatment options for resistance or relapse to crizotinib include ceritinib, cytotoxic chemotherapy, palliative radiotherapy, or supportive care.

None of the above agents are approved with a REMS or a Boxed Warning. Interstitial lung disease, bradycardia, embryo-fetal toxicity, and hepatotoxicity are common adverse events labeled in the Warnings & Precautions section for crizotinib and ceritinib, and will also be labeled for alectinib. QT interval prolongation is listed as a Warning and Precaution for both crizotinib and ceritinib. Severe or persistent GI toxicity, hyperglycemia, and pancreatitis are adverse events listed in the Warnings and Precautions for ceritinib; however these events were not seen with alectinib or crizotinib. Severe visual loss is also a Warning and Precaution with crizotinib, but this adverse event was not seen for alectinib or ceritinib.

When comparing alectinib with crizotinib and ceritinib for treatment of ALK-positive mNSCLC, there were lower incidences of ILD and hepatic transaminase increases with alectinib as compared to crizotinib and ceritinib in clinical trials. However, myalgia and increased CPK elevations were seen more in the alectinib clinical trials versus crizotinib and ceritinib. These adverse events will be communicated in the Warnings and Precautions section of the label.

The primary adverse events of concern for alectinib were hepatoxicity, interstitial lung disease, bradycardia, and severe myalgia and CPK elevation. The Division determined the adverse events of hepatotoxicity, ILD, bradycardia, severe myalgia and increased CPK elevation to be adequately addressed under the Warnings & Precautions section of the label. Two of the adverse events, hepatoxicity and bradycardia, can be monitored. Instructions on monitoring for hepatotoxicity and bradycardia will be included in the label under Warnings and Precautions. The effect of alectinib on CNS activity was assessed, however for crizotinib and ceritinib, the data was limited and a comparison could not be made with those drugs. For alectinib, it was shown that the CORR was 61% and the CDOR was 9.1 which were both considered clinically meaningful.

The likely prescribing population for alectinib and management of patients who are candidates for alectinib will be oncologists in the outpatient setting. A Patient Information Sheet will be included in labeling. These prescribers are familiar with the disease and adverse events seen with drugs used for the treatment of ALK –positive mNSCLC who have progressed on crizotinib.

5 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

FDA is currently in the process of negotiating with the applicant on a postmarketing requirement to submit the results of at least one multicenter, randomized clinical trial establishing the superiority of alectinib over available therapy in patients with ALK-positive mNSCLC. At this time, the milestone dates have not been determined.

6 CONCLUSION

DRISK and DOP-2 concur that at this time a REMS for alectinib is not necessary to ensure that the benefits outweigh the risks for the treatment of patients with ALK-positive, mNSCLC who have progressed on crizotinib. The risks associated with alectinib

treatment will be communicated through professional labeling and routine pharmacovigilance. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

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/s/

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11/06/2015

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