CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208434Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	NDA 208434
Applicant	Hoffmann-La Roche Inc.
Date of Submission	July 6, 2015
PDUFA Goal Date	March 4, 2016
Proprietary/Established Name	Alecensa/alectinib
Dosage Form(s) / Strength(s)	capsules for oral administration/150 mg
Applicant Proposed Indication(s)	Treatment of patients with anaplastic lymphoma (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
Recommended Action for NME:	Accelerated Approval.
Recommended Indication	Treatment of adult patients with ALK-positive, metastatic NSCLC who have progressed on, or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Patricia Keegan
Regulatory Project Manager	Gina Davis
Medical Officer Review	Erin Larkin
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	Eias Zahalka, Kimberly Ringgold, Whitney Helms, John Leighton
OPQ Review	Olen Stephens, Charles Jewell, Rajiv Agarwal, Zhaoyang Meng, Zhong Li, Gerlie Gieser
Clinical Pharmacology Review	Stacy S. Shord; Jingyu (Jerry) Yu; Ping Zhao
OPDP Review	Nazia Fatima
OSI Review	Lauren Iacono-Connors
OSE/DMEPA Review	Grace P. Jones
OSE/DRISK Review	Mona Patel
DPMH Review	Suchitra M. Balakrishnan
Patient Labeling Review	Rowell Medina & Nazia Fatima
Associate Director for Labeling Review	Jennie Chang
CDTL Review	Gideon Blumenthal

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Metastatic, anaplastic lymphoma kinase (ALK) mutation-positive, non-small cell lung cancer (NSCLC) is genetically distinct form of lung cancer that is not curable with available therapy. Based on the National Institute of Health (NIH) Surveillance, Epidemiology and End Results (SEER) Program, an estimated 9,400 patients were expected to be diagnosed with ALK mutation-positive NSCLC in 2015. Crizotinib, which is indicated the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test, is the current first-line therapy administered in such patients, however acquired resistance to crizotinib develops, usually after several months of treatment. The median survival in patients with metastatic ALK mutation-positive NSCLC was 20.8 months in patients receiving crizotinib as first-line therapy, thus confirming the life-threatening nature of this subtype of NSCLC.

Alectinib is the second kinase inhibitor with a broader spectrum of activity against multiple ALK mutations that has demonstrated durable objective responses in patients with ALK mutation-positive NSCLC whose disease had progressed on crizotinib therapy, likely due to development of additional mutations in ALK and/or other genes. Although not directly compared in a randomized clinical trial, alectinib has demonstrated a numerically higher overall response rate (ORR) than was demonstrated in clinical trials reviewed by FDA for other drugs approved broadly for the second-line treatment of NSCLC (docetaxel alone or with ramucirumab, pemetrexed, and nivolumab). Demonstration of the treatment effect was descriptive; however it meets the criteria for substantial evidence of a treatment effect as the results are similar in two separate, multicenter trials (Studies NP28761 and NP28673). These trials demonstrated an ORR of 44% (95% CI: 36%, 53%) and of 38% (95% CI: 28%, 49%) with median duration of response of 7.5 months and 11.2 months in 87 patients (Study NP28761) and 138 patients (Study NP28673), respectively, in patients with ALK mutation-positive NSCLC that had progressed on crizotinib or who were unable to tolerate crizotinib. These data are further supported by evidence of clinically meaningful ORR in the subset of 110 patients enrolled in Study NP28673 who had progressed on crizotinib and received prior platinum-based chemotherapy, where the ORR was 39% (95% CI: 30, 49) and the median duration of response was 10.9 months. In addition, there was evidence of antitumor activity in central nervous system (CNS) metastases, a common site of metastases and disease progression where effective drug delivery across the blood brain barrier is likely to impact tumor control. Among patients identified as having measurable CNS disease, the CNS response rate was 57% (95% CI: 39%, 74%) with median durations of CNS response of 9.1 months in Study NP28673 and the ORR was 69% (95% CI: 41%, 89%), where the median duration of response was not estimable, in Study NP28761.

The clinical safety experience is very limited (253 patients), and uncommon serious adverse reactions (occurring at an incidence of ≤1%) may be identified in the post-marketing setting. However, based on the current data, the risks of alectinib are qualitatively similar to that occurring with other FDA-approved drugs in this class (ALK inhibitors) or with other anti-neoplastic agents approved for treatment of NSCLC. The most common adverse reactions of alectinib were fatigue (41%), constipation (34%), edema (30%) and myalgia (29%). Across both trials, 23% required at least one dose reduction for adverse reactions with a median time to first dose reduction of 48 days. The most common adverse reactions resulting in dose reductions or interruptions of dosing were hyperbilirubinemia (6%), elevated CPK levels (4.3%), elevated ALT levels (4.0%), elevated AST levels (2.8%), and vomiting (2.8%). The incidence of serious adverse reactions requiring dose modifications is approximately 23%, which is not unusual for anti-neoplastic agents. Dose modifications were generally successful in the management of serious, including fatal, adverse reactions of hepatotoxicity, ILD, severe myalgia and

CPK elevation, and bradycardia. The serious risks of alectinib are qualitatively similar and not substantially higher in incidence than those observed with other products in the class (crizotinib and ceritinib) or other antineoplastic agents, which based on post-marketing experience, can be safely administered without REMS.

The effect of alectinib on durable ORR has been demonstrated and is numerically better than that achievable with FDA-approved therapy. Based on prior experience with crizotinib, an effect on ORR of sufficient magnitude and duration is likely to predict an effect on progression-free survival (PFS). The risks of alectinib are acceptable in this patient population, where the potential for an improvement in a median survival for less than 2 years would be considered to outweigh risks that can be generally managed with dose modification. Therefore, I have concluded the risk:benefit profile is favorable, as have Drs. Keegan, Blumenthal and Larkin.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	ALK mutation-positive NSCLC has both distinct clinical and pathologic characteristics, occurring at a younger median age and in non-smokers and females more commonly than in those with NSCLC without ROS-1, RET, or ALK mutations. Patients with ALK mutation-positive lung cancers are more likely to have extracellular mucin, cribriform pattern, signet ring cells and hepatoid cytology on pathologic evaluation.[1] There is no evidence that the presence of ALK mutations confer a better prognosis.[1, 2] However, with the advance of effective therapy inhibiting kinase activation, specifically crizotinib, PFS is improved as compared to first-line, platinum-based doublet chemotherapy [HR 0.45 (0.35, 0.60); median PFS 10.9 vs. 7.0 months] or second-line pemetrexed or docetaxel [HR 0.49 (0.37, 0.64); median PFS 7.7 vs. 3.0 months] and median survival of 20.8 months for those receiving crizotinib as second-line therapy and compared with reported median survivals of 9.1 months with docetaxel alone or 10.5 months with docetaxel and ramucirumab.[3,4] While there are no good estimates of the estimated 5-year survival rate of patients with metastatic, ALK mutation-positive NSCLC, available therapy indicates that the disease is not curable, and there remains an unmet need for this life-threatening form of cancer.	Metastatic, ALK mutation-positive, NSCLC is genetically distinct form of lung cancer that is not curable with available therapy.

[1] ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: A comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. Pan Y, Zhang Y, Li Y, et also. Lung Cancer (84):121–126, 2014.
[2] Clinical characteristics associated with ALK rearrangements in never-smokers with pulmonary adenocarcinoma. Sun JM, Lira M, Pandya K, et al. Lung Cancer (83) 259–264, 2014.
[3] http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202570s014lbl.pdf
[4] http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125477s011lbl.pdf

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	There are no FDA-approved drugs indicated for the treatment of patients with ALK-mutation-positive NSCLC who are no longer responding to or are intolerant of crizotinib. • Ceritinib, which is indicated for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib, was approved under accelerated approval; therefore, ceritinib is not considered to be available therapy as the clinical benefit of the durable ORR observed with ceritinib has not been verified. • Similarly, pembrolizumab was approved for the treatment of PD-L1 positive NSCLC under accelerated approval and is also not considered available therapy. FDA approved therapy for the second-line treatment of NSCLC that have been evaluated in patients with ALK mutation-positive NSCLC: • Docetaxel or pemetrexed as second-line chemotherapy following platinum-based doublet chemotherapy. In patients with ALK-mutation-positive NSCLC receiving second-line therapy in a randomized trial comparing the efficacy of platinum-based chemotherapy with crizotinib, demonstrated an ORR of 20% (14, 26) with a median duration of response of 5.6 months. The following FDA-approved regimens are approved for the second-line treatment of NSCLC. • Ramucirumab with docetaxel has not been evaluated in studies of ALK mutation-positive NSCLC. In studies of patients with NSCLC receiving second-line chemotherapy, after platinum-based doublet chemotherapy, the ORR was 23% (95% CI: 20, 26) in patients randomized to ramucirumab plus docetaxel and 14% (95% CI: 11, 17) in patients receiving placebo plus docetaxel.[5] • Nivolumab has not been evaluated in studies of ALK mutation-positive NSCLC. In studies of patients with NSCLC receiving second-line chemotherapy, after platinum-based doublet chemotherapy, the ORR was 19% (95% CI: 15, 24) in patients randomized to nivolumab and 12% (95% CI: 9, 17) in patients randomized to docetaxel.	There are no drugs with regular FDA approval for the treatment of patients with ALK-mutation- positive NSCLC who are no longer responding to or are intolerant of crizotinib

[5] http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125477s011lbl.pdf

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	In two single-arm, multicenter trials, treatment with alectinib 600 mg orally twice daily demonstrated an ORR of 44% (95% CI: 36%, 53%) and 38% (95% CI: 28%, 49%) with a median duration of response of 7.5 months and 11.2 months as determined by an independent radiologic review committee in 87 patients (Study NP28761) and 138 patients (Study NP28673), respectively, in patients with ALK mutation-positive NSCLC that had progressed on crizotinib or who were unable to tolerate crizotinib. Among the 110 patients enrolled in Study NP28673 who had progressed on crizotinib and received prior platinum-based chemotherapy, there were 43 patients who achieved a partial response, for an ORR of 39% (95% CI: 30, 49) and a median duration of response 10.9 months. In addition, to the ORR, evidence of reduction in CNS tumor burden was also observed, with a CNS response rate as determined by independent review (per RECIST) in patients with measurable CNS metastases at study entry of 57% (95% CI: 39%, 74%) with a median duration of CNS response of 9.1 months in Study NP28673 (n=35) and 69% (95% CI: 41%, 89%) where the median duration of response was not estimable, in Study NP28761 (n=16).	Based on the data provided in this NDA, alectinib provides a clinically meaningful improvement in durable ORR as compared to the FDA-approved therapies for the second-line treatment of NSCLC (nivolumab, docetaxel alone or with ramucirumab, and pemetrexed), including the subset of patients in Study NP28673 (n=110) receiving third-line therapy for ALK mutation positive NSCLC. Based on clinical trials in the first-line setting with another ALK inhibitor (crizotinib), an improvement in ORR and duration of response over available therapy [platinum-based chemotherapy] was subsequently shown to lead to clinically important improvements in PFS.
Risk	The clinical safety experience is very limited (253 patients), thus uncommon serious adverse reactions, occurring at an incidence of ≤1%, may be identified in the post-marketing setting. The most common adverse reactions of alectinib were fatigue (41%), constipation (34%), edema (30%) and myalgia (29%). Across both trials, 23% required at least one dose reduction for adverse reactions with a median time to first dose reduction of 48 days. The most common adverse reactions resulting in dose reductions or interruptions of dosing were hyperbilirubinemia (6%), elevated CPK levels (4.3%), elevated ALT levels (4.0%), elevated AST levels (2.8%), and vomiting (2.8%). Fatal adverse reactions occurred in 2.8% of the 253 patients enrolled in Studies NP28761 and NP28673; these fatal events were hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%), pulmonary embolism (0.4%), and endocarditis (0.4%); however, as there is no comparator arm, it is difficult to place these fatal adverse reactions in the context of the disease setting. The most serious adverse reactions of alectinib are hepatotoxicity, interstitial lung disease, muscular toxicity manifesting as increased in CPK and severe myalgia, and bradycardia. Other areas of concern, which did not present as serious adverse reactions in Studies NP28761 and NP28673, are photosensitivity and visual defects, but which would be of concern if it occurred at a greater severity.	The risks of alectinib are qualitatively similar to that occurring with other FDA-approved drugs in this class (ALK inhibitors) or with other anti-neoplastic agents approved for treatment of NSCLC. The incidence of serious adverse reactions requiring dose modifications is approximately 23%, which is not unusual for anti-neoplastic agents. Dose modifications were generally successful in the management of serious, including fatal, adverse reactions of hepatotoxicity, ILD, severe myalgia and CPK elevation, and bradycardia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	The NDA did not contain proposed Risk Evaluation and Mitigation Strategies (REMS). Hoffmann-La Roche proposed to manage risks through product labeling and routine post-marketing surveillance.	The serious risks of alectinib are qualitatively similar and not substantially higher in incidence than those observed with other products in the class (crizotinib and ceritinib) or other antineoplastic agents, which based on post-marketing experience, can be safely administered without REMS.

2. Background

On June 26, 2013, FDA designated alectinib as a Breakthrough Therapy for the treatment of patients with ALK-positive NSCLC that had progressed on crizotinib therapy.

On July 6, 2015, Hoffmann-La Roche submitted the NDA for alectinib, an NME, for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib.

3. Product Quality

There are no CMC issues that would preclude approval. The Office of Process and Facilities recommends approval of the manufacturing and testing sites based on inspectional findings.

Alectinib will be marketed as an immediate-release capsule as a single strength (150 mg alectinib free base). An expiration period of 24 months is granted when stored in 250 mL round, 240-count white HDPE bottles with child resistant closures when stored below 30 ^{O}C and protected from light.

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical issues that preclude approval. The NDA contained the results of nonclinical in vitro and in vivo pharmacology studies supporting proposed mechanism of action of alectinib as a reversible inhibitor of the ALK and the re-arranged during transfection (RET) kinases at concentrations achieved with the recommended dose, with suppression of ALK phosphorylation.

The nonclinical, 13-week toxicology studies conducted in rats and monkeys were considered relevant based on evidence that the metabolism, distribution, protein binding, and elimination of alectinib were similar to that observed in humans. The concentrations of the alectinib and the major active metabolite (M4) in rats exceeded those achieved with the recommended human dose and in monkeys were approximately half those achieved in humans. Toxicities observed in animals were qualitatively similar to those observed in humans, with pathologic findings in the adrenal gland, gastrointestinal (GI) tract, liver, reproductive system (testes, epididymis, seminal vesicles, and prostate) and respiratory system (lung and trachea). In addition, toxicology studies in rats revealed adverse effects on teeth and growing bones, which were considered potentially relevant to the pediatric population (and thus described in Section 8.4 of product labeling), but not for the indicated population, as ALK-positive NSCLC occurs only in adults. Clinical findings included evidence of hemorrhage in the GI tract and intestinal perforation. Clinical laboratory findings included increases in creatinine, cholesterol, triglyceride, alkaline phosphatase isoenzymes, increases in reticulocytes, platelets, and neutrophils, decreases in hematocrit and hemoglobin, and increased APTT and PT in rats.

Safety pharmacology studies and nonclinical studies demonstrated hypotension and bradycardia, which have been observed in clinical studies, but no evidence of QT prolongation and a negative hERG assay. Evidence of phototoxicity (also observed in clinical studies) was demonstrated in a cytotoxicity assay model.

Alectinib is clastogenic in the micronucleus assay with an increase in the chromosome number but was not mutagenic. Pilot embryofetal toxicology studies demonstrated embryofetal toxicity and maternal toxicity at exposures of 2.9-fold and 2.7-fold, in rabbits and rats respectively, compared with exposures achieved with the recommended human dose. Effects included fetal loss and low fetal weight in species, dilated ureter, thymic cord, small ventricle and thin ventricle wall, and reduced number of sacral and caudal vertebrae in rats, and retroesophageal subclavian artery in rabbits. Since ALK signaling appears to be important in early neurologic development, this potential concern was noted in product labeling. Based on the positive findings in these pilot studies, further embryofetal development studies were not required. In addition, based on the proposed indication and current 5-year survival rates, carcinogenicity studies and fertility studies were not required.

5. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that would preclude approval. The proportion of patients requiring dose modification for adverse reactions was 23%, indicating that the majority of patients are able to tolerate the proposed dosage regimen. There was no exposure–response (E-R) relationship that was identified for efficacy or toxicity among patients receiving alectinib 600 mg BID, supporting the dosage regimen.

Alectinib exhibits dose-proportional pharmacokinetics (PK) over the dose range of 400 to 600 mg BID and both alectinib and its major active metabolite (M4) are bound to human plasma proteins (>99%). The absolute bioavailability of alectinib is 37% under fed conditions in healthy subjects. Alectinib reached maximal concentrations after approximately 4 hours and exhibited a geometric mean elimination half-life of 32 hours for alectinib and 31 hours for M4 following administration of alectinib at the recommended dose in patients with ALK-positive NSCLC. The dosing schedule of twice daily dosing was selected to avoid an increased incidence of higher adverse reactions at the maximal concentrations which would be achieved following a single daily dose of 1200 mg; based on its half-life, there is no need to make up missed doses of alectinib.

There was a clinically significant effect on alectinib exposure when taken with or without food. In a food effects study conducted in 18 healthy volunteers receiving a single dose, the individual and combined exposures of alectinib and of M4 were increased by approximately 3-fold when alectinib was taken with a high-fat meal compared to those when alectinib was taken under a fasted state. Clinical studies supporting efficacy directed patients to take alectinib with food and this recommendation has been included in product labeling. There were no clinically important effects of concurrent administration of pH inhibitors on the pharmacokinetics of alectinib or M4.

In mass balance studies, the liver appears to be the major elimination pathway with 98% of a radiolabeled dose eliminated in the feces. Both alectinib and its major active metabolite, M4, are metabolized by CYP3A4. However, based on drug interaction studies conducted with alectinib and either rifampin or posoconazole, no dose adjustment is needed for patients taking a CYP3A4 modulator.

Based on the popPK analysis, no dose adjustment of alectinib is needed in patients based on age, gender, body weight, mild hepatic impairment, mild to moderate renal impairment (CLcr 30 to 89 mL/min), or race (White, Asian and Other). The PK of alectinib and M4 have not been studied in patients with severe renal impairment, end-stage renal disease or moderate to severe hepatic impairment. Since alectinib is primarily metabolized by the liver, a post-marketing study is required to assess the PK and provide recommendations on a reasonably safe dose of alectinib in patients with moderate or severe hepatic impairment but were not required for renal impairment based on the lack of effects on PK in patients with mild to moderate renal impairment and the minor role, if any, of renal metabolism of alectinib.

Based on serial ECGs obtained in 221 patients receiving alectinib at the recommended dose, there was no evidence of a clinically important increase in QTc.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

There are no outstanding clinical efficacy issues that would preclude approval. This NDA was supported by the results of two multicenter (Study NP28761 and NP28673), single arm, open-label clinical trials in patients with metastatic ALK rearrangement-positive NSCLC who had progressed on or were intolerant to the ALK inhibitor crizotinib (Study 1 and 2) and the majority also received previous systemic chemotherapy. All patients received alectinib 600 mg twice daily. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.1 as evaluated by an

independent review committee (IRC) and by Investigator. Additional outcome measures included duration of response (DOR), central nervous system (CNS) ORR according to RECIST v1.1 in patients with baseline measurable lesions in the CNS, and CNS DOR.

Study NP28761 (n=87) showed an ORR of 38% (95% CI: 28%, 49%) by IRC and 46% (95% CI: 35%, 57%) by Investigator. In Study NP28673 (n=138), the ORR was 44% (95% CI: 36%, 53%) by IRC and 48% (95% CI: 39%, 57%) by Investigator. The median DOR was 7.5 months in Study NP28761and 11.2 months in Study NP28673 after a median duration of follow-up of 4.8 months and 10.9 months, respectively. In a pooled analysis of patients from Study NP28761and Study NP28673 with baseline measurable lesions in the CNS, the CNS ORR was 61% (95% CI: 46%, 74%) and the median CNS DOR was 9.1 months.

Efficacy Analyses in Studies NP28761 and NP28673				
Efficacy Parameter	Study NP28761 (N=87)		Study NP28673 (N=138)	
	IRC* Assessment	Investigator Assessment	IRC* Assessment	Investigator Assessment
Objective Response Rate (95% CI)	38% (28; 49)	46% (35; 57)	44% (36; 53)	48% (39; 57)
Number of Responders	33	40	61	66
Median Duration of Response (months); (95% CI)	7.5 (4.9, NE)	NE (4.9, NE)	11.2 (9.6, NE)	7.8 (7.4, 9.2)

Pooled Analysis of CNS ORR and Duration of Response in Patients with Measurable CNS Lesions at Entry	
Efficacy Parameter	N=51
CNS Objective Response Rate (95% CI)	61% (46, 74)
Complete Response	18%
Partial Response	43%
Median Duration of CNS Response (months (95% CI)	9.1 (5.8, not evaluable)

Among the 110 patients enrolled in Study NP28673 who had progressed on crizotinib and received prior platinum-based chemotherapy, there were 43 patients who achieved a partial response, for an ORR of 39% (95% CI: 30, 49) and a median duration of response 10.9 months.

In response to FDA's request for information regarding the safety and efficacy of administration of alectinib to patients who were intolerant of crizotinib, data on 5 such crizotinib-tolerant patients receiving alectinib across the clinical development program were submitted. These data supported the conclusion that patients unable to tolerate crizotinib due to hepatotoxicity or pulmonary toxicity/pneumonitis, could tolerate alectinib. In four of these 5 patients, the investigator identified partial responses were observed with median durations of 2.8, 2.8, 12.8+, and 15.4 months.

8. Safety

Safety data was evaluated in 253 patients who received alectinib at a dose of 600 mg twice daily. The most common adverse reactions were fatigue, constipation, edema, and myalgia. The majority of these adverse reactions were grade 1-2. The most common grade 3-4 adverse reaction was dyspnea. The most common laboratory abnormalities were anemia, elevations in aspartate aminotransferase (AST), elevations in alkaline phosphatase, and elevations in creatine phosphokinase (CPK). The majority of the above laboratory abnormalities were grade 1-2. The most common grade 3-4 laboratory abnormalities were elevations in alanine aminotransferase (ALT), lymphopenia, and elevations in CPK.

Serious adverse events (SAEs) were reported in 19% of patients. The most common SAEs (reported in 3 patients each) included dyspnea, pulmonary embolism, and elevations in bilirubin. The most frequent adverse reactions leading to dose reductions or interruptions were elevations in bilirubin, CPK, ALT, AST, and vomiting. The most common adverse events leading to discontinuation included ALT elevations (1.6%), and bilirubin elevations (1.6%). Fatal adverse events occurred in 2.8% of patients, including 1 case each of hemorrhage and intestinal perforation attributed to alectinib.

9. Advisory Committee Meeting

This NDA was not referred to an ODAC because it is not the first drug in its class, the safety profile is acceptable for the proposed indication, the clinical trial design is similar to that used for accelerated approval for patients with NSCLC with no satisfactory alternative therapy, the application did not raise safety or efficacy in the intended patient population, and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Alectinib was granted orphan drug designation for the treatment of ALK-positive NSCLC and is therefore exempt from PREA requirements.

11. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)
  A REMS is not required.

- Other Postmarketing Requirements and Commitments
  See action letter.

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

/s/

TAMY E KIM
12/11/2015

RICHARD PAZDUR
12/11/2015