

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202570Orig1s000

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

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 11, 2011

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Subject: Review of the risks associated to NME Crizotinib

Drug Name
(Established Name): Crizotinib

Therapeutic Class: Anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and a hepatocyte growth factor receptor (HGFR, c-Met) RTK inhibitor

Dosage and Route: 200 mg and 250 mg capsules, oral

Application Type/Number: NDA 20-2570

Applicant: Pfizer Inc.

OSE RCM #: 2011-1135

1. INTRODUCTION

This review provides DRISK's recommendations based on the safety data submitted by the sponsor in support of NDA 20-2570, crizotinib.

On September 13, 2010, crizotinib received an orphan-drug designation and was reviewed under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*.

Crizotinib is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants and an inhibitor of the hepatocyte growth factor receptor (HGFR, c-Met) RTK. Crizotinib is indicated for the treatment of ALK-positive non-small cell lung cancer (NSCLC). Crizotinib is not authorized or licensed in any country.

The sponsor proposed to manage all identified risks through labeling; a Risk Evaluation and Mitigation Strategy (REMS) was not included in the submission.

2. MATERIALS REVIEWED

The following documents were reviewed:

- Pfizer, Crizotinib, Clinical Safety Summary, March 2, 2011, submitted March 30, 2011.
- Pfizer, Crizotinib, proposed Prescribing Information (PI), submitted March 30, 2011 and FDA revised label from August 3, 2011.

3. RESULTS OF REVIEW

3.1 Overview of the Clinical Program

The clinical development program for crizotinib included a total of 8 studies:

- **Study A8081001** – an ongoing multicenter, multinational, open-label, single-arm study evaluating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer, including a cohort of patients with ALK-positive advanced NSCLC.
- **Study A8081005** – multicenter, multinational, open-label, single-arm, Phase 2 study evaluating the safety and efficacy of crizotinib in patients with ALK-positive advanced NSCLC.
- **Six, phase 1 clinical pharmacology studies** – total of 6 biopharmaceutics and clinical pharmacology studies conducted in healthy volunteers (study details provided in the Clinical Safety Summary, section 2.7.4, Table 1, page 15).

A total of 450 subjects were included in these 8 studies. Two hundred fifty five patients with ALK-positive NSCLC were treated with crizotinib. Data from ALK-positive subjects included in studies A8081001 and A8081005 were pooled to allow composite analysis. However, the primary analyses of safety were performed in studies A8081001 and A8081005 individually since studies used different common toxicity criteria

versions.¹ The pooled data analyses did not adjust for these differences. In addition, Serious Adverse Event (SAE) reports obtained from an ongoing study (A80811007, a multicenter, multinational, open-label, randomized Phase 3 study comparing crizotinib to pemetrexed or docetaxel in patients with previously treated ALK-positive advanced NSCLC) were described by the sponsor.

3.2 Important Safety Concerns

Most adverse events (AEs) reported were mild to moderate (Grade 1 or Grade 2). The most commonly reported AEs were gastrointestinal, neurological, visual, constitutional, and hepatic in nature. Twenty-four percent of the patients reported SAEs, the most common Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PT) were PT Disease Progression (3.9%) and PT Pneumonia (3.9%). Two of the 22 in-study deaths (1 death due to pneumonitis, 1 death of unknown cause) were considered crizotinib-related.

The sponsor identified several safety issues based on their clinical significance or frequency of observation in the clinical trials and potential attribution to treatment with crizotinib. These included pneumonitis, QT interval prolongation, increases in serum transaminases, neutropenia, gastrointestinal disorders, neuropathy, and visual disorders.

Following is a brief description of the safety concerns.

- **Pneumonitis** – Four subjects presented with potentially drug-induced pneumonitis, including 1 death. Crizotinib has been associated (frequency <2%) with severe, life-threatening pneumonitis in the above mentioned clinical trials. The background incidence rate of pneumonitis or interstitial lung disease in retrospective studies and clinical studies of advanced NSCLC patients ranges from 3.0% to 47.0% in patients receiving chemotherapy or radiation therapy and from 0.2% to 3.0% in patients receiving epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitor (TKI) or placebo.²
- **QT Interval Prolongation** - Prolongation of the QTcF interval ≥ 500 (Fridericia's correction) was reported in 1.2% of subjects in studies A8081001 and A8081005. There were 4 (1.6%) patients with reported AEs coded as "Electrocardiogram QT prolonged". However, there was 1 treatment-related SAE of QTc prolongation in study A8081007. A substudy of A8081007, designed to characterize the effects of therapy with crizotinib on QTc, is ongoing.
- **Hepatic Enzyme Elevation:** AE reports describing increases in ALT were received from subjects participating in Studies A8081001 (4.2%) and A8081005 (4.4%). These reactions were generally asymptomatic, had a positive dechallenge, and did not recur at lower crizotinib doses. However, 2 patients required permanent discontinuation of therapy. Increases in ALT >3 X ULN and total bilirubin >2 X ULN without elevated

¹ National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 3.0 was used in Study 1001 and Version 4.0 in Study 1005. NCI CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline: Grade 1 Mild AE; Grade 2 Moderate AE; Grade 3 Severe AE; Grade 4 Life-threatening or disabling AE; Grade 5 Death related to AE

² Pfizer, Crizotinib, Clinical Safety Summary, March 2, 2011, submitted March 30, 2011

alkaline phosphatase were detected in 1/225 (< 0.5%) of patients with available laboratory data across both studies. There was 1 patient in Study A8081001 who experienced hepatic dysfunction meeting Hy's Law criteria.

- **Neutropenia:** Severe and life-threatening neutropenia (Grade 3 or 4) was reported in studies A8081001 (3.4%) and A8081005 (2.2%). There were no deaths or SAEs reported in association to neutropenia. However, there was 1 case of PT Fungal infection reported in association with treatment-related Grade 4 Neutropenia in Study A8081005.
- **Vision Disorders:** Included PT Diplopia, PT Photopsia, PT Vision blurred, PT Visual field defect, PT Visual impairment, and PT Vitreous floaters. Although frequent, vision disorders were mild in severity and did not required dosing interruption, dose reduction, or permanent discontinuation from study treatment. The sponsor recommends having an ophthalmological evaluation only if the symptoms persist or worsen in severity.
- **Edema:** Reports of edema including PT Localized oedema, PT Oedema, PT Oedema peripheral, were frequent but mild to moderate in nature. There was a treatment-related SAE reported (PT Oedema peripheral) in study A8081005, but there was no need to discontinue crizotinib permanently.
- **Neuropathy:** Treatment-related mild to moderate neuropathy was reported by 11% of patients in both studies. Previous therapy with platinum could be a confounding factor.
- **Gastrointestinal Disorders:** The most commonly reported gastrointestinal AE were PT Nausea, PT Diarrhea, PT Vomiting, PT Constipation, and esophageal disorders (PT Dysphagia, PT Epigastric discomfort, PT Gastroesophageal reflux disease, PT Odynophagia, PT Oesophageal obstruction, PT Oesophageal pain, PT Oesophageal spasm, PT Oesophageal ulcer, PT Oesphagitis, PT Reflux oesophagitis). These were mainly mild in severity and its prevalence decreased after 3-4 weeks of crizotinib therapy.

4. DISCUSSION

Lung cancer is the leading cause of cancer death for both men and women; approximately 85% of lung cancers are NSCLC.³ Crizotinib's proposed indication is for a narrowly defined patient population; specifically patients who have anaplastic lymphoma kinase (ALK)-positive advanced NSCLC. ALK-positive patients are the only ones for whom crizotinib demonstrated a benefit. FDA agrees with the sponsor on the inclusion of a warning indicating that detection of ALK-positive NSCLC is necessary for selection of patients treated with crizotinib.

Non-clinical studies in rats and rabbits showed that crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg BID. Based on these data, the FDA designated

³ American Cancer Society- Lung Cancer <http://www.cancer.org/Cancer/LungCancer-Non-SmallCell/OverviewGuide/index> revised 6/20/2011 accessed August 9, 2011.

crizotinib as Pregnancy Category D. A warning regarding potential fetal harm will be added to the *Warnings and Precautions* section of the label.

The Food and Drug Administration Amendments Act (FDAAA) of 2007 gives FDA authority to require a REMS if a strategy beyond routine labeling is required to ensure the benefits of the drug outweigh the risks.

Most, if not all of the prescribers of crizotinib will be oncologists who are experienced and familiar with prescribing as well as monitoring and managing similar serious adverse events that are associated with antineoplastic therapy. DRISK concurs with DDOP that the serious adverse events of neutropenia, pneumonitis, QT interval prolongation, and increases in transaminases are consistent with risks associated with other antineoplastic agents and managed by oncologists without a REMS and therefore can be adequately addressed by inclusion in the *Warnings and Precautions* section of the label along with guidelines for dosage modifications or interruptions based on the severity of hematological, pulmonary, cardiac or liver toxicities.

In clinical trials, crizotinib demonstrated antitumor efficacy for the treatment of ALK-positive advanced NSCLC. At this time, the benefits of crizotinib appear to outweigh the risks in a defined patient population with advanced disease, the decision to not require a REMS is reasonable based on the current risk-benefit profile.

5. RECOMMENDATIONS

DRISK recommends managing all identified serious safety risks through labeling. Additional risk management strategies such as a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use do not appear warranted at this time. DRISK will provide additional comments and recommendations if the review division has further concerns with the risks outlined above, or identifies additional risks associated with crizotinib warranting more extensive risk mitigation.

Please notify DRISK if you have any questions.

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/s/

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