# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 201292Orig1s000

# 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: | April 24, 2013 |
| Reviewer(s): | Suzanne Robottom, Pharm.D.<br>Division of Risk Management (DRISK) |
| Team Leader: | Cynthia LaCivita, Pharm.D.<br>DRISK |
| Division Director: | Claudia Manzo, Pharm.D.<br>DRISK |
| Subject: | Review evaluates if a risk evaluation and mitigation strategy (REMS) is needed |
| Drug Name(s): | afatinib tablets |
| Therapeutic Class: | EGFR tyrosine kinase inhibitor |
| Dosage and Route: | 40 mg orally once daily |
| Application Type/Number: | NDA 201292 |
| Applicant/sponsor: | Boehringer Ingelheim Pharmaceuticals, Inc. |
| OSE RCM #: | 2012-2792; 2798 |

# 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for afatinib. The applicant did not submit a proposed REMS or risk management plan.

## 1.1 BACKGROUND

Lung cancer is the leading cause of cancer death in the US. The five-year relative survival rate from 1995 to 2001 was 15.7%; this rate varies depending on stage of diagnosis. There are two main categories, "small cell" and "non-small cell." Non-small cell lung cancer (NSCLC) is more common.[1] In patients with locally advanced or metastatic NSCLC systemic platinum-based chemotherapy is considered the first-line treatment of choice.[2]

Afatinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor and is proposed as treatment of patients with locally advanced or metastatic NSCLC with EGFR mutations.

Afatinib binds to the kinase domain of EGFR resulting in the down regulation of signaling from ErbB family members. These receptors are expressed on the cell surface of both normal and cancer cells and signaling through these receptors plays a role in cell survival and proliferation.

The proposed dose is 40 mg orally once daily.

## 1.2 OTHER PRODUCTS IN THE SAME THERAPEUTIC CLASS/THERAPEUTIC ALTERNATIVES

According to the National Cancer Institute, the following are the *targeted* therapies that are also FDA-approved for the treatment of NSCLC:

- Gefitinib (Iressa; initial approval May 5, 2003)
- Bevacizumab (Avastin; initial approval February 26, 2004)
- Crizotinib (Xalkori; initial approval August 26, 2011)
- Erlotinib (Tarceva; initial approval November 18, 2011)

### 1.2.1 Known Adverse Events

The following table provides an overview of the approved indication, mechanism of action, and Warnings listed in labeling for the above reference treatment options for NSCLC.

[1] www.cancer.gov; accessed April 22, 2013.

[2] March 29, 2013 Center Director Briefing Background document.

| Drug | FDA-Approved Indication | Mechanism of Action | Warnings |
|---|---|---|---|
| Gefitinib (Iressa) | Monotherapy for the continued treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies … . | Inhibits phosphorylation of numerous tyrosine kinases including those with EGFR | • Pulmonary Toxicity<br>• Pregnancy Category D<br><br><u>Precautions</u><br>• Hepatotoxicity |
| Bevacizumab (Avastin) | Treatment of non-squamous NSCLC with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease | Inhibits vascular endothelial growth factor (VEGF)-specific angiogenesis | • GI perforation[BW]<br>• Surgery and wound healing complications[BW]<br>• Hemorrhage[BW]<br>• Non-GI fistula formation<br>• Arterial thromboembolic events<br>• Hypertension<br>• Reversible posterior leukoencephalopathy syndrome<br>• Proteinuria<br>• Infusion reactions<br>• Ovarian failure<br>• Pregnancy Category C |
| Crizotinib (Xalkori) | Kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic NSCLC that is ALK positive as detected by an FDA-approved test | Inhibits tyrosine kinase receptors including ALK, HGRF, RON. | • Hepatotoxicity<br>• Pneumonitis<br>• QT internal prolongation<br><br>• Pregnancy Category D |
| Erlotinib (Tarceva) | Monotherapy indicated for the maintenance treatment of patients with locally advance or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.<br><br>Monotherapy indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. | Inhibits phosphorylation of tyrosine kinase associated with EGFR. | • Pulmonary Toxicity<br>• Renal failure<br>• Hepatotoxicity<br>• GI perforation<br>• Bullous and exfoliative skin disorders<br>• MI/Ischemia<br>• Cerebrovascular accident<br>• Microangiopathic hemolytic anemia with thrombocytopenia<br>• Ocular disorders<br>• Potential bleeding<br><br>• Pregnancy Category D |

[BW] The risk is a Boxed Warning.

None of these products have a REMS or Medication Guide to address the serious safety concerns associated with these products.

## 2 MATERIALS REVIEWED

- Midcycle meeting slides. February 7, 2013.
- Avastin [package insert]. South San Francisco, CA: Genentech, Inc.;2013
- Tarceva [package insert]. Farmingdale, NY: OSI Pharmaceuticals, LLC, Inc.; 2012
- Xalkori [package insert]. New York, NY: Pfizer; 2013.
- Iressa [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2004.

## 3 RESULTS OF REVIEW

### 3.1 OVERVIEW OF CLINICAL PROGRAM

Please refer to the clinical review by Dr. Shakun Malik, MD for the full review of the safety and efficacy.

Afatinib (n=229) was evaluated as first- line therapy in a phase III (LUX-LUNG 3) randomized, open-label trial vs pemetrexed/cisplatin (n=111) in patients with metastatic adenocarcinoma of the lung with EGFR mutation positive with no previous treatment with EGFR tyrosine kinase inhibitors. The primary endpoint was progression-free survival (PFS; independent review). Overall survival was a secondary endpoint. Patients treated with afatinib had a median PFS of 11.1 months compared to 6.9 months in the pemtrexed/cisplatin arm (additional 4.2 months PFS) which was statistically significant. There was no statistical difference in OS (28.1 vs 28.2 months, respectively).

The majority of patients had an EGFR mutation categorized as 'Common' (89.3%), comprising Exon 19 Deletion alone (49.3%) or Exon 21 L858R alone (40.0%). All 'Other' patients (10.7%, 26 afatinib patients, 11 chemotherapy patients) had EGFR mutations comprising 10 different genetic subtypes. While the overall primary endpoint demonstrated improved PFS for patients treated with afatinib, on subset analysis, there is a possibility of a detrimental effect on PFS in the "other" EGFR mutation subtype. In light of these data, the indication will include a limitation of use that the safety and efficacy have not been established in patients whose tumors have other EGFR mutations.

### 3.2 SAFETY CONCERNS

The following risks are included in the Warnings section of the FDA draft labeling (as of April 9, 2013):


- Keratitis: Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in (0.8%) of patients treated with BRAND among 3865 patients across clinical trials. Keratitis was reported in 5 (2.2%) of patients in Study 1 with Grade 3 in 1 (0.4%).


In summary, the following table (presented at the midcycle meeting Dr. Shakun Malik) provides an overview of the serious adverse experienced in patients treated with afatinib compared to pemetrexed/cisplatin. A lower percentage of patients discontinued treatment due to drug related adverse events (7.9% vs 11.7%) and a similar percentage of patients experienced a drug-related serious adverse event (14.4%). More patients died from drug-related fatal adverse events compared to no deaths in the pemetrexed/cisplatin arm.

| | Afatinib 40 mg N = 229 11.7 mo* | Pem/Cis N = 111 3.7 mo* |
|---|---|---|
| | All AEs, % | |
| Any AEs | 100.0 | 98.2 |
| Grade 3 | 51.1 | 44.1 |
| Grade 4 | 3.9 | 9.9 |
| AEs leading to dose reduction | 57.2 | 16.2+ |
| AE leading to discontinuation | 14.0 | 15.3 |
| Due to drug-related AEs | 7.9 | 11.7 |
| Serious AE | 28.8 | 22.5 |
| Drug-related SAEs | 14.4 | 14.4 |
| AE leading to death | 5.7 | 2.7 |
| Drug-related fatal AEs | 1.7 | 0 |

## 4 DISCUSSION

Afatinib prolongs progression-free survival by 4.2 months compared to platinum-based chemotherapy.

In general, the risks associated with afatinib treatment are consistent with other approved targeted drugs for the treatment of NSCLC (hepatic, dermatologic, pulmonary, cardiac, ocular, and fetal toxicity) or with tyrosine kinase inhibitors (specifically EGFR inhibitors – diarrhea, dermatologic, ocular, cardiac). None of these other treatment options are approved with a REMS to manage the serious risks associated with the drug products.

Despite these serious adverse events, in the phase 3 clinical trial a lower percentage of patients treated with afatinib compared to pemetrexed/cisplatin discontinued treatment due to drug-related adverse events.

DRISK does not recommend a REMS to address any of the risks associated with afatinib at this time. Based on the available data, severity of the disease, treatment alternatives and their associated toxicities, familiarity of these adverse drug events and appropriate management within the prescribing population, and the potential benefit of afatinib these risks can be adequately addressed through labeling, including the limitation to use for common mutations, at this time. This view is shared by the Division of Oncology Products (DOP 2).

## 5 CONCLUSION

In conclusion, DRISK and DOP2 agree that a REMS is not required for afatinib at this time. If new safety information becomes available or use includes a new patient population, the risk-benefit of this drug should 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/

---

SUZANNE C BERKMAN ROBOTTOM
04/24/2013

CLAUDIA B MANZO
04/24/2013
concur