CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201292Orig1s000

OFFICE DIRECTOR MEMO

Office Director Summary Review

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	201292
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	November 15, 2012
PDUFA Goal Date	July 15, 2013
Proprietary Name / Established (USAN) Name	GILOTRIF Afatinib
Dosage Forms / Strength	Tablet / 20, 30, and 40 mg tablets
Proposed Indication(s). *See approved labeling for final approved indication.*	"for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test *[see Clinical Studies (14.1, 14.2)]"*
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director Review	Patricia Keegan
Regulatory Project Manager Review	Deanne Varney
Medical Officer Review	Shakun Malik
Statistical Review	Jonathan Norton
Pharmacology Toxicology Review	Denali (Dubravka) Kufrin & Shawna Weis
CMC ONDQA Reviews	Haripada Sarker, Li-Shan Hsieh, Ali Al Hakim
Biopharmaceutics Review	Elsbeth Chikhale
Clinical Pharmacology Review	Runyan Jin
OPDP Reviews	Quynh-Van Tran (DPDP) & Karen Dowdy (DMPP)
OSI Review	Lauren Iacono-Connors
CDTL Review	Anthony Murgo
OSE/DMEPA Consult	James Schlick
OSE/DRISK Consult	Suzanne Robottom
Maternal Health Consult	Tammie Brent Howard

OND=Office of New Drugs
CMC= Chemistry, Manufacturing and Controls OSE= Office of Surveillance and Epidemiology
OPDP= Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSI= Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE=Office of Surveillance and Epidemiology
DRISK=Division of Risk Management
DMEPA= Division of Medication Error Prevention and Analysis

1. Introduction

On November 15, 2012, Boehringer Ingelheim submitted this New Drug Application (NDA) for Gilotrif (afatinib), which is a tyrosine kinase inhibitor that covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in down regulation of ErbB signaling.

The clinical development program in NSCLC included two trials conducted in patients with NSCLC containing an EGFR mutation as detected by a PCR-based investigation assay who had not received prior treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and two trials conducted in patients who were "clinically enriched" for EGFR mutations but had not been tested and who had received treatment with an EGFR TKI. The latter trials were considered flawed in that the clinical enrichment strategy did not correlate with subsequent EGFR mutation testing. In addition, of the two trials conducted in this population, the randomized trial in this population failed to meet its primary endpoint. Therefore, only studies conducted in patients who were screened for EGFR mutations prior to enrollment were evaluated for efficacy claims.

2. Background

There will be an estimated 228,190 new cases of lung cancer (approximately 85% are expected to be NSCLC) and 159,480 deaths from lung cancer in 2013[1]. Based on SEER data[2], the estimated 5-year survival rate for patients with metastatic lung cancer is less than 5%. While standard treatment with a platinum-based chemotherapy doublet regimen was considered standard first-line therapy for all patients with NSCLC, emerging evidence has identified subpopulations based on histopathologic diagnosis (e.g., pemetrexed[3]) or molecular abnormalities (crizotinib[4]) where tumor-based outcomes are superior with targeted therapy.

Available Therapy

Erlotinib: On May 14, 2013, the approved indication for erlotinib was expanded to include the first-line treatment of metastatic NSCLC whose tumors have an epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 substitution (L858R) mutations. This approval was supported by a single, randomized (1:1), open-label, active-controlled trial (EURTAC trial) in 174 patients receiving first-line treatment for metastatic NSCLC whose tumors had EGFR exon 19 deletion or exon 21 substitution (L858R) mutation as detected by a clinical trial assay.

The EURTAC trial demonstrated a statistically significant improvement in investigator-determined progression-free survival (PFS) for patients randomized to erlotinib compared to those randomized chemotherapy [Hazard ratio (HR) 0.34 (95% confidence intervals (CI): 0.23, 0.49), $p<0.001$] with a doubling of the median PFS from 5.2 months in the chemotherapy arm to 10.4 months in the erlotinib arm. There was no statistically significant difference in survival between the TARCEVA and chemotherapy arms. The overall response rate (ORR) was substantially higher (65% vs. 19%) for the erlotinib arm compared to the chemotherapy arm.

Drugs approved for the first-line treatment of metastatic NSCLC, without consideration of EGFR mutation status, are following: paclitaxel protein-bound particles, crizotinib, pemetrexed, paclitaxel, bevacizumab, gemcitabine, vinorelbine, methotrexate.

The standard of care in the United States (for more than a decade) for treatment of NSCLC was platinum-based doublet chemotherapy. In 2002, there were published results of a 4-arm, open-label, randomized (1:1:1:1) trial.

[1] http://www.cancer.gov/cancertopics/types/lung. Accessed March 2, 2013.
[2] http://seer.cancer.gov/statfacts/html/lungb.html. Accessed March 2, 2013
[3] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/021462s015ltr.pdf. Accessed March 2, 2013
[4] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/202570s000ltr.pdf. Accessed March 2, 2013

The "control" arm was the paclitaxel/carboplatin arm and the regimen for which paclitaxel is approved for the treatment of NSCLC. The trial demonstrated similar outcomes for the following doublet chemotherapies:

- Cisplatin plus paclitaxel (control), cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus paclitaxel.

The authors concluded that all the combinations have similar efficacy.[5] However, the Eastern Collaborative Oncology Group (ECOG) selected carboplatin/paclitaxel as its reference regimen for future studies due to a more favorable safety profile.

3. CMC/Biopharmaceutics

There are no issues that preclude approval for CMC/biopharmaceutics. CMC reviewers have provided an overall acceptability for the manufacturing of drug product and drug substance.

The drug product, Gilotrif, will be supplied as film-coated tablets in the following strengths. The proposed dissolution methodology, the dissolution acceptance criterion, and the comparative dissolution profiles between the drug product used in the pivotal trial and the proposed commercial drug product were determined to be acceptable. The quality of commercial afatinib tablets was determined to be acceptable based on assessment of the manufacturing process and process controls and analytical procedures for identification, purity, strength, and stability. Stability testing supports an expiry of 24 months.

4. Nonclinical Pharmacology/Toxicology

There are no issues that preclude approval for nonclinical pharmacology/toxicology.

In nonclinical models, afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation of cell lines expressing wild-type EGFR and in cell lines expressing EGFR exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutation. Afatinib also inhibited *in vitro* proliferation of cell lines over-expressing HER2.

The primary general toxicology studies were conducted in rats and minipigs. The toxicologic findings mirrored the human safety profile, with evidence of gastrointestinal, cutaneous, ocular (corneal atrophy), renal, and pulmonary parenchymal toxicity observed in one or both species tested. In safety pharmacology studies, decreased left ventricular ejection fraction was observed in minipigs receiving afatinib at a dose of 30 mg/kg, which correlated with observations in clinical trials. The evaluation for effects on electrophysiology (*in vitro* hERG testing and *in vivo* ECG monitoring in minipigs and rats) were consistent with studies in human subjects, indicating that risk of QT prolongation at the recommended human dose/exposures were low.

Based on reproductive toxicity studies in rats and rabbits, embryofetal toxicity is predicted at the recommended dose and expected exposure with afatinib in humans. Nonclinical studies demonstrated an increased risk of abortion, increased risk of resorption, visceral and skeletal variations (delayed ossification), and lower fetal weights. Studies in female rats also suggested impairment of fertility based on the observation of decreased number of corpora lutea and increases in pre-implantation loss and early resorptions at exposures expected in humans and by effects on reproductive organs observed in the general toxicology studies. Afatinib was present at high concentrations in the milk of lactating rats.

In a dedicated fertility study, evidence of effects on male fertility were identified which included epithelial atrophy and a dose-dependent increase in the incidence of hypospermia.

[5] Schiller JH, Harrington D, Belani CP, et al: Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 346:92-98, 2002.

Based on the totality of the *in vitro* testing, including conflicting results between the Ames and other tests, neither afatinib nor its major metabolites are considered to be genotoxic.

5. Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval.

The median time to reach peak plasma concentration (T_{max}) was 5 hours after a single oral dose and 3 hours after multiple doses of afatinib. Steady state was attained following 8 days of afatinib administered daily. The elimination half-life was 21-27 hours after a single dose and 45 hours at steady state. The relative bioavailability was 92% (90% CI: 76%, 112%) based on $AUC_{0\text{-}inf}$ after a single dose of 20 mg tablet compared to an oral solution. A mass balance study suggested that the major route of excretion of afatinib was via feces (85%) while 4% in urine.

Based on the population PK analysis, weight, gender, age, and race do not have clinically relevant effects on afatinib exposure. Formal organ impairment studies were not submitted in the NDA and were initially not considered necessary based on the metabolism of afatinib and on the summary results of the population PK analysis. There were no clinically significant differences in exposure between patients with normal, mild or moderate hepatic impairment. In the population PK studies, mild renal impairment has no effect on afatinib systemic exposure and the increases in trough concentrations with moderate renal impairment not considered clinically important based on overall population PK analyses, However, based on a re-analysis of data from Study 1200.32, limited to patients receiving afatinib at 40 mg daily, a clinically important increase in trough concentrations were identified among patients with renal impairment; this has been noted in product labeling and will be further evaluated in a formal organ impairment study to be conducted under a post-marketing requirement.

Based on the regimen used in Study 1200.32, BI proposed a recommended dose of afatinib 40 mg orally once daily, (b) (4) However, in Study 1200.32, only 16 of the 229 patients randomized to afatinib and receiving at least one dose of study drug underwent escalation to the 50 mg dose; of these, 10 were unable to tolerate dosing at 50 mg daily. In addition, the analysis assessing the exposure-response relationship suggests that the 50 mg daily dose does not result in better or similar efficacy. Specifically, in the exposure-efficacy analyses assessing outcomes by exposure quartile in Study 1200.32, patients in the highest quartile for steady state AUC had shorter progression-free survival times as compared to other quartiles – this decrement in PFS was clinically important and similar to that observed in the control arm, suggesting loss of treatment effect. In addition, the results of logistic regression analyses suggested that higher exposure of afatinib increased the risk of experiencing an adverse reaction of NCI CTCAE grade 3 severity or grade 2-3 diarrhea.

In food-effects studies, afatinib exposure was decreased (39% in $AUC_{0\text{-}inf}$ and 50% in C_{max}) after a high-fat meal as compared to that under the fasted condition. Product labeling reflects this information and provides dosing recommendations that afatinib to be taken at least one hour before or two hours after a meal.

Based on evaluation for possible drug interactions, product labeling includes recommendations for reduction in the dose of afatinib in patients who require concomitant P-gp inducers or inhibitors since afatinib is both a substrate and inhibitor of the P-gp transporter. Specifically, clinically important changes in afatinib exposure were observed when afatinib was administered with ritonavir (a P-gp inhibitor) or rifampicin (a P-gp inducer).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

BI relied primarily on the results of four clinical trials to support labeling claims in both patients who had and who had not received prior treatment with an EGFR tyrosine kinase inhibitor (TKI). The major efficacy trial supporting the recommendation for approval is summarized below. Issues relating to study design and outcomes for the three supportive trials (LUX-1, LUX-2, and LUX-5) are also briefly described below.

Primary Trial to Support NDA– Study 1200.32 (LUX-3):
The primary trial supporting this NDA was Study 1200.32 (LUX-3), a randomized, open-label, multicenter, multinational trial comparing the efficacy of afatinib to cisplatin/pemetrexed chemotherapy doublet for the first-line treatment of metastatic or unresectable, EGFR mutation-positive adenocarcinoma of the lung. In this trial, 345 patients were randomized (2:1) to receive afatinib 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was PFS as assessed by an independent review committee (IRC). The key secondary efficacy endpoints were ORR and OS. The characteristics for the study population were 65% female, median age of 61 years, baseline ECOG performance status of 0 (39%) or 1 (61%), and 26% Caucasian and 72% Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to afatinib [HR 0.58 (0.43, 0.78), $p < 0.001$], with median PFS of 11.1 months in the afatinib arm and 6.9 months in the chemotherapy arm. There was no statistically significant difference for OS between the treatment arms at the interim analysis conducted at 84% of the planned events for the final analysis [HR 0.91 (0.66, 1.25), p=0.55], with a median survival of 28 months in each arm. As the median survival is longer than anticipated with platinum-doublet chemotherapy, cross-over to the afatinib arm may have obscured possible effects of afatinib on survival. In addition, the afatinib also had substantially higher ORR (50% vs. 19%). In exploratory analyses, treatment effects varied by the underlying EGFR mutation, with the greatest treatment effect in the subgroup with exon 19 deletions for both PFS and OS and a more modest, but clinically important effect for those with exon 21 L858R substitutions, but with apparent harmful effects for patients with uncommon EGFR mutations receiving afatinib as compared to those receiving chemotherapy.

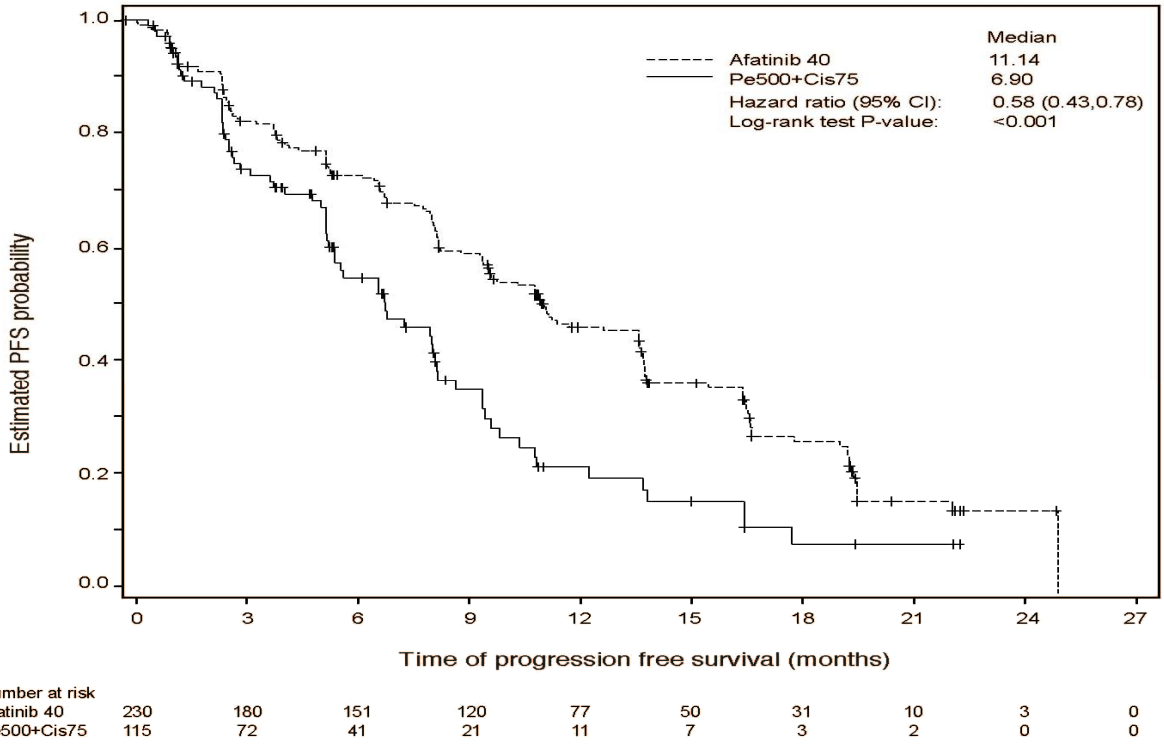
The results of Study 1200.32 provide substantial evidence of effectiveness of afatinib in this patient population. A statistically significant and clinically important improvement in PFS, as determined by the IRC, was demonstrated for patients randomized to afatinib compared to those randomized to chemotherapy, however there was no statistically significant difference for OS between the treatment arms at the interim analysis conducted at 84% of the planned events for the final analysis. The key efficacy results are provided in the following table and the Kaplan-Meier curves for PFS are presented in the figure following the table.

Table 1: Efficacy Results of Study 1

	BRAND (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-free Survival		
Number of Deaths or Progressions, N (%)	152 (66.1%)	69 (60.0%)
Median Progression-free Survival (months)	11.1	6.9
95% CI	(9.6,13.6)	(5.4,8.2)
HR (95% CI)	0.58 (0.43, 0.78)	
Stratified Log-Rank Test P-value*	<0.001	
Overall Survival		
Number of Deaths, N (%)	116 (50.4%)	59 (51.2%)
Median Overall Survival (months)	28.1	28.2
95% CI	(24.6,33.0)	(20.7,33.2)
HR (95% CI)	0.91 (0.66, 1.25)	
Stratified Log-Rank Test P-value*	0.55	
Objective Response Rate (CR + PR)		
N (%)	116 (50.4%)	22 (19.1%)
Response Duration		
Median (months)	12.5	6.7

*Stratified by EGFR mutation status and race.
CR=complete response; PR=partial response

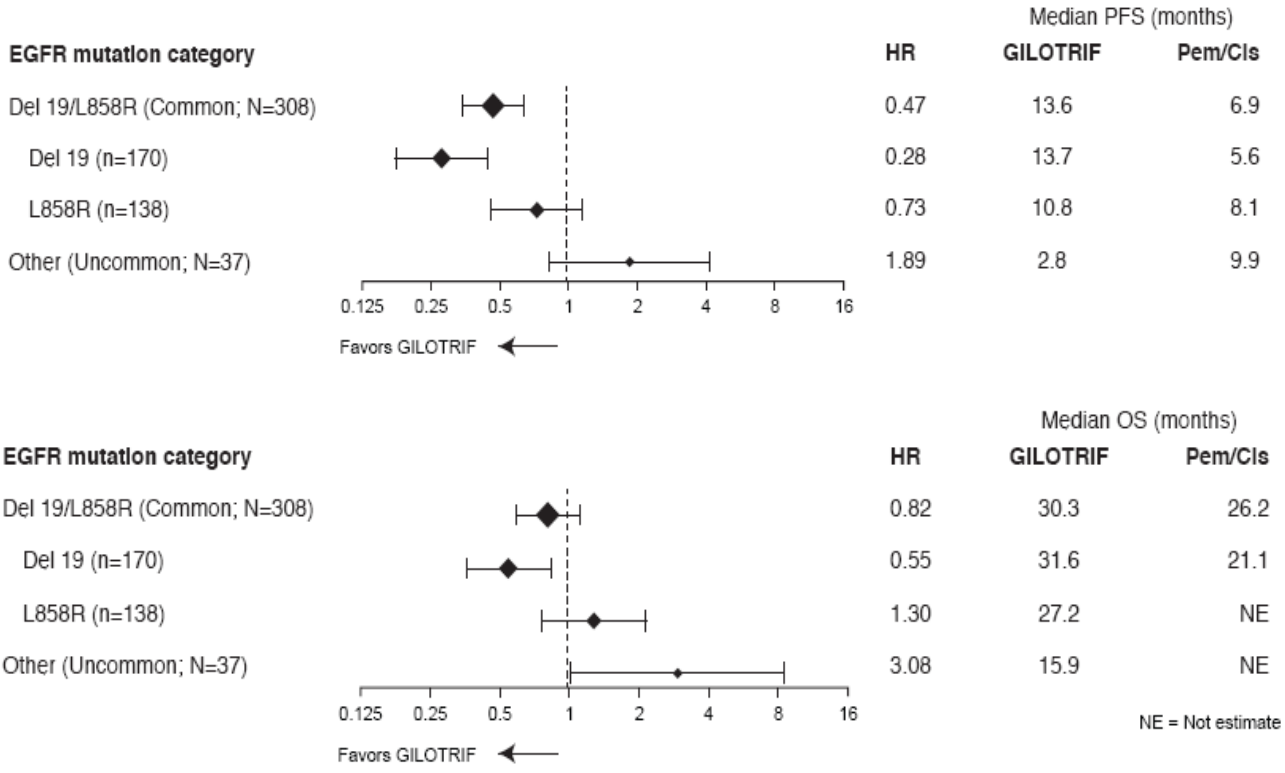
Figure 1 Kaplan-Meier Curve for PFS by Independent Review by Treatment Group



Exploratory analyses by EGFR mutation type
Tumor samples from 264 patients (178 randomized to afatinib and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic *therascreen*® EGFR RGQ PCR Kit, which will be approved concurrent with the approval of afatinib. The treatment effects of afatinib were similar in this subpopulation identified by the to-be-marketed companion diagnostic as those observed with the clinical trial assay.

The clinical trial stratified randomization by EGFR mutation type (exon 19 deletions vs. exon 21 L858R substitution vs. other mutations) using the clinical trials assay. Based on concerns that the treatment effect may differ based on the underlying mutation, FDA performed exploratory subgroup analyses for PFS and OS based on the stratification factor of EGFR mutation status and on the subgroup of "common" mutations for which afatinib will be indicated. These data are displayed in the Forest plots, taken from the product labeling and reproduced below.

Figure 2 Forest plot of PFS and OS for Common (Del19, L858R) and Uncommon (other) EGFR Mutation Categories



Based on these analyses, FDA concluded that the treatment effect is dependent on the underlying EGFR mutation. While PFS and OS show a consistent improvement for afatinib-treated patients, those with "other" mutations show a consistent and worse outcome when receiving afatinib as compared to standard chemotherapy. Similar findings were observed in an additional study of afatinib submitted to the IND (i.e., favorable treatment effects in patients with exon 19 deletions or exon 21 L858R substitutions but not in pooled analyses of patients with other less common mutations). These findings do not rule out the possibility that other less common mutations may benefit however there is insufficient data provided in the NDA to identify such subgroups.

To further investigate the possibility of benefit is specific less common mutations, FDA evaluated the ORR in patients with these less common mutations. There were 26 afatinib -treated patients in the "other" (uncommon) EGFR mutations subgroup with nine unique mutation patterns. Of the 26 afatinib-treated patients in the "other" EGFR mutation subgroup, four (15%) achieved a partial response and of the 11 chemotherapy-treated patients in

the "other" EGFR mutation subgroup, four (36%) achieved a partial response. Among the afatinib-treated patients, at least one patient with mutations in L858R and T790M, L858R and S768I, S768I alone, or G719X alone achieved a partial response; information on the response rate observed in patients with these mutations are displayed in the table below, reproduced from the product labeling. No responses were seen in afatinib-treated patients with the following mutations: T790M alone (n=2), deletion 19 and T790M (n=3), G719X and T790M (n=1), exon 20 insertion (n=6), and L861Q alone (n=3).

Table 2 Objective Tumor Responses in GILOTRIF-Treated Patients Based on Investigator Assessment in the "Other" (uncommon) EGFR Mutation Subgroup

EGFR Mutations	Number of GILOTRIF-Treated Patients	Number of Patients with Partial Responses	Duration of Response
L858R and T790M	5	1	6.9 months
L858R and S768I	2	1	12.4+ months
S768I	1	1	16.5+ months
G719X	3	1	9.6 months

+ Censored observation

The results of Study 1200.32 provide substantial evidence of the effectiveness of afatinib for the first-line treatment of patients with EGFR mutation-positive NSCLC. Exploratory subgroups by EGFR mutation type were conducted by FDA to evaluate for differential treatment effects which may correlate with *in vitro* assessments of inhibitory capacity by mutation site. Although exploratory, the consistency observed for differential treatment effect by mutation type for PFS and OS and the high-level results submitted to the IND for an additional randomized trial of afatinib in a similar population suggest that these findings are real. Such information is important to prescribers and patients to characterize treatment outcomes and will be useful as new agents against this target are developed.

Additional Trials Boehringer Ingelheim intended to Support NDA:
Trials intended to support claims for afatinib in the treatment of patients with NSCLC who have not received prior EGFR TKI therapy

- LUX-Lung 2: Open-label, single-arm, activity-estimating trial conducted in 129 patients with locally advanced or metastatic lung adenocarcinoma containing an EGFR mutation who had not received prior EGFR TKI therapy. EGFR mutation status was evaluated by PCR testing with a clinical trials assay. Approximately half of these patients received no prior chemotherapy (n=61) and the remainder received only one prior line of chemotherapy (n=68) (i.e., after failure of first-line chemotherapy). Approximately three-quarters of the patients received afatinib at a dose of 50 mg daily (n=99) and the remaining 30 patients received afatinib 40 mg daily. The primary endpoint of the trial was determination of overall response. Based on independent review, BI reported that the ORR in the first-line setting was 66% with a median duration of 13.5 months, while the ORR in the second line setting was 57% with a median duration of response of 12.9 months. While these data are supportive, they do not extend the clinical efficacy data described in Study 1200.32 and as a single arm trial, they are not deemed more reliable.

Trials intended to support claims in patients with NSCLC who have received prior EGFR TKI therapy

- LUX-Lung 1: This was a randomized (2:1), placebo-controlled trial conducted in 585 patients receiving third or fourth line treatment for NSCLC; al1 patients had previously received 1 or 2 lines of chemotherapy, one of which was required to have been a platinum-containing regimen, and to have progressed after treatment with

an EGFR-TKI (either gefitinib or erlotinib). Of the 585 patients, 390 were randomized to receive afatinib 50 mg daily and 195 patients were randomized to matching placebo. Patients were not screened for the presence of EGFR mutations but were considered to be clinically enriched for EGFR mutations by requiring patients to have had prior EGFR-TKI therapy for at least 12 weeks. The primary endpoint in this study was OS with a secondary endpoint of PFS.

The study population demographics were female (59%), median age of 61 years, baseline ECOG performance status of 0 or 1 (92%), either White (33%) or Asian (66%). All patients were required to have received prior platinum-containing regimen, 60% had 1 line and 39% had 2 lines of prior chemotherapy for metastatic disease. All patients had received prior EGFR TKI therapy, consisting of erlotinib (55%), gefitinib (40%) or both (5%). The trial failed to meet its primary endpoint of improved survival with a median survival of 10.8 months for afatinib-treated patients and 12.0 months for patients in the placebo arm. Therefore, the effects on PFS cannot be considered statistically significant and an improvement in median PFS time of 2.2 months for afatinib (median PFS 3.3 months) as compared to placebo (median PFS 1.1 months) is of unclear clinical importance. Similarly, the higher response rate observed with afatinib is not clinically meaningful as it remains less than 10%.

- LUX-Lung 5: This was an open-label, randomized, multicenter trial conducted in 1154 patients with patients with unresectable or metastatic NSCLC. Eligibility criteria were similar to those in the LUX-1 trial. All patients received afatinib 50 mg daily; at the time of disease progression, the subgroup deemed to have clinical benefit (without disease progression for ≥12 weeks) received afatinib 40 mg daily plus paclitaxel or to receive investigator's choice chemotherapy.

(b) (4)

FDA did not consider the LUX-5 study adequate in design as the patient population enrolled did not correlate with EGFR mutation status. Further, the restrospective analyses conducted are considered exploratory, at best, and do not meet the criteria for substantial evidence of effectiveness as described in FDA's Guidance on Clinical Effectiveness for Drugs and Biologics.

(b) (4)

8. Safety

There was adequate evaluation of safety, with data from more than 3800 patients across multiple clinical trials, including 2135 patients which NSCLC. In addition, safety data were available from randomized, controlled trials of 229 afatinib-treated patients with EGFR mutation-positive, metastatic, non-squamous, NSCLC who were enrolled in Study 1200.32. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m² followed after 30 minutes by cisplatin 75 mg/m² every three weeks for a maximum of six treatment courses. The median exposure to afatinib was 11.0 months and to pemetrexed/cisplatin chemotherapy was 3.4 months. The overall trial population had a median age of 61 years, 64% of patients who received afatinib and 67% of patients who received pemetrexed/cisplatin were female, and 70% of patients who received afatinib and 72% who receive pemetrexed/cisplatin chemotherapy were Asian. Serious adverse reactions were reported

in 29% of patients treated with afatinib. The most frequent serious adverse reactions reported in patients treated with afatinib were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in afatinib -treated patients in Study 1200.32 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Dose reductions due to adverse reactions were required in 57% of afatinib-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with afatinib were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%).

Discontinuation of therapy in afatinib-treated patients for adverse reactions was 14%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%).

Post-marketing Surveillance
Based on the Nonclinical Pharmacology review, a theoretical risk of idiosyncratic drug reactions, specifically hemolysis, was identified. The potential for this risk is based on the binding of afatinib to hemoglobin. The OSE review staff will be alerted to this potential risk so that monitoring can be targeted for this event.

REMS
Both the clinical review team and DMEPA agreed that a REMS was not required to ensure safe and effective use of afatinib.

9. Advisory Committee Meeting

This application was not referred to ODAC because outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion. The clinical study design was acceptable and the application did not raise significant safety or efficacy issues in the intended population.

10. Pediatrics

Orphan designation was granted for afatinib on December 3, 2012 for "treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer (NSCLC) as detected by an FDA-approved test," therefore afatinib is exempt from the requirements of PREA for this indication.

11. Labeling

- Proprietary name: The proprietary name GOLTRIF submitted March 4, 2013 was determined to be acceptable.

- Physician labeling- All major issues were resolved, and a summary of clinically important modifications are discussed by labeling section, below.
  - Indications and Usage: The proposed indication was limited to first-line treatment and to the specific EGFR mutations (exon 19 deletions or exon 21 L858R substitution) where efficacy has been established. Added limitation of use stating that the efficacy of afatinib has not been established for other EGFR mutations.
  - Dosage and Administration: Added a new subsection denoting that companion diagnostic test should be used to identify patients for whom afatinib is indicated. (b) (4) (b) (4) (b) (4) Added specific dose

modifications for afatinib when given with a P-gp inhibitor or with a P-gp inducer based on the PK data submitted in the NDA.

- Clinical Studies: The results from Studies LUX-2, LUX-1, and LUX-5 were not included in product labeling since FDA concluded that these studies did not provide substantial evidence of effectiveness. Results of health-related quality of life obtained in Study 1200.32 were not included in product labeling as these are exploratory analyses obtained in an open-label trial. Analyses in subsets based on EGFR mutation type are included in labeling as these are clearly identified as exploratory; in addition, randomization was stratified for this variable, preserving principles of randomization, the results were consistent across endpoints (PFS and OS), other studies of afatinib (IND studies), and other products in this class (erlotinib). Information on uncommon mutations were provided for information only and to aid prescribers in providing information to patients.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment: Unresectable or metastatic NSCLC is a serious and life-threatening disease; there is only one other drug which has been approved (erlotinib) for treatment of NSCLC containing exon 19 deletions or exon 21 L858R EGFR mutations. Based on the results of Study 1200.32, afatinib treatment demonstrated a statistically robust and clinically important improvement in PFS for patients randomized to afatinib compared to those randomized to chemotherapy [HR 0.58 (95% CI:.43, 0.78), p<0.001] with an approximate doubling of the median PFS from 6.9 months in the chemotherapy arm to 11.1 months in the afatinib arm. There was no statistically significant difference in OS between the afatinib and chemotherapy arms, with 84% of the planned events, however effects on survival, if any, may have been obscured by the high rate of post-progression use of an EGFR inhibitor for patients in the chemotherapy arm. In addition, ORR was substantially higher (50% vs. 19%) for the afatinib arm compared to the chemotherapy arm.

  There was adequate evaluation of safety, with data from more than 3800 patients across multiple clinical trials. In Study 1200.32, the most common adverse reactions (≥20%) are diarrhea, rash, stomatitis, paronychia, dry skin, dermatitis acneiform, decreased appetite, and pruritus. Serious adverse reactions were reported in 29% of patients treated with afatinib. The most frequent serious adverse reactions reported in patients treated with afatinib were diarrhea (6.6%), vomiting (4.8%), and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in afatinib-treated patients in Study 1200.32 consisted of interstitial lung disease (1.3%), sepsis (0.43%), and pneumonia (0.43%).

  Substantial evidence of effectiveness (an improvement in PFS of a clinically important magnitude) was demonstrated in this trial. While an improvement in OS has been used as the basis for most recent drug approvals for the treatment of NSCLC, treatment effects of this magnitude are also considered to be evidence of clinical benefit provided that the risks are acceptable. The risk:benefit profile has also been assessed by Drs. Keegan, Murgo and Malik, and I concur with their recommendation, as well as other discipline reviewer recommendations to approve this application.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  A REMS is not required to ensure safe use or mitigate severe adverse reactions for afatinib for the proposed indication.

- Recommendation for other Postmarketing Requirements and Commitments: See action letter.

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/s/

TAMY E KIM
07/11/2013

RICHARD PAZDUR
07/11/2013