CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201292Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 201292, Gilotrif (afatinib)
Product Name:

PMR/PMC Description: Pharmacokinetic Trial of Moderate and Severe Renal Impairment

PMR/PMC Schedule Milestones:

Final Protocol Submission:	(b) (4)
Study/Trial Completion:	9/15/2014
Final Report Submission:	(b) (4)
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

In the registration trial it was observed that the median trough afatinib plasma concentrations in patients with mild and moderate renal impairment were 27% and 85% higher than those in patients with normal renal function, respectively. Patients with severe renal impairment may have even higher afatinib exposures, which could cause more toxicity.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical pharmacokinetic trial is to determine the appropriate afatinib doses in patients with moderate and severe renal impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a pharmacokinetic trial to determine the appropriate doses of afatinib in patients with moderate and severe renal impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

RUNYAN JIN
07/02/2013

HONG ZHAO
07/02/2013
I concur.

JEFFERY L SUMMERS
07/03/2013

PMR/PMC Development Template
NDA 201292

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Ttrial Completion:	N/A
	Final Report Submission:	April 30, 2014.
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☒ Life-threatening condition
   ☒ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Afatinib approval for the indication will be based on the FDA data review of Study1200.32.

In the study, patients (n=345) with EGFR mutation-positive, metastatic non-squamous, NSCLC were randomized (2:1) to receive Afatinib 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115).

The study met its primary endpoint of PFS showing a statistically significant and clinically meaningful 4.2 month improvement in the median PFS between patients treated with Afatinib as compared to patients treated with chemotherapy [11.1 months vs. 6.9 months [HR 0.58; 95% CI 0.43, 0.78; p-value 0.0003 (log-rank test)].

There was no statistically significant difference for overall survival between the treatment arms at the interim analysis (based on 84% of OS planned number of events).

FDA PMC is to review the final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

RCT

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

DEANNE R VARNEY
06/19/2013

JEFFERY L SUMMERS
06/19/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: May 13, 2013

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari, PhD, DABT
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, MD
Associate Director, OND
Pediatric and Maternal Health Staff

To: Division of Oncology Products 2 (DOP2)

Drug: Afatinib (BRAND) NDA 201292

Subject: Afatinib is a new molecular entitiy (NME) submitted for NDA approval

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

Materials Reviewed: Afatinib product labeling and available literature regarding pregnancy and lactation

Consult Question: DOP2 requested assignment of a PMHS-MHT reviewer to attend milestone meetings and to provide labeling comment for this new NDA.

INTRODUCTION

Boehringer Ingelheim Pharmaceuticals, Inc (BIPI) submitted a New Drug Application (NDA) for Afatinib Tablets on November 14, 2013. Afatinib is a New Molecular Entity (NME) with a proposed indication for treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations(s).

Afatinib is a kinase inhibitor that covalently binds to the kinase domain of EGFR and irreversibly inhibits the tyrosine kinase autophosphorylation of the ErbB receptor family (EGFR, HER2, HER4) resulting in downregulation of signaling. Afatinib demonstrated inhibition of cell growth in NSCLC cell lines (*in vitro)* with wild-type EGFR or with exon 21 (L858R) or T790M mutations and demonstrated anti-tumor activity in xenografts or transgenic tumor models.

The Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DOP2 on November 21, 2012 to attend milestone meetings during the review cycle and provide labeling comments for this new NDA. This review includes PMHS-MHT comments and recommendations for Afatinib labeling.

BACKGROUND

Afatinib and Pregnancy

Afatinib is an NME and there are no human pregnancy data available. In animal developmental reproductive studies, Afatinib was embryotoxic and led to abortions at late gestational stages in rabbits at doses resulting in exposures approximately 0.2 times the human exposure by AUC at the recommended human dose of 40 mg daily or greater. There were developmental toxicities, in the presence of maternal toxicity, consisting of reduced fetal weights, increased incidence of runts, visceral and dermal variations. In rats, at doses resulting in exposures 2 times the human exposure at the recommended human dose, there were skeletal alterations including incomplete or delayed ossifications and reduced fetal weights. These data are reported in current afatinib labeling.

Afatinib and Lactation

It is not known if afatinib is present in human milk. Afatinib was present in the milk of lactating rats at concentrations 80-150 times higher than those found in plasma from 1 to 6 hours after administration. A search of the Micromedex, LactMed and PubMed databases revealed no human data regarding afatinib and lactation. In addition, there are no available human lactation data for other kinase inhibitors regarding effects on nursing infants.

REVIEW OF SUBMITTED MATERIALS

Sponsor Proposed Afatinib Labeling

The PMHS-MHT reviewed the sponsor's proposed afatinib labeling, submitted November 14, 2012 and participated in several labeling/team meetings during the review period. A summary of

PMHS-MHT labeling recommendations appear immediately following Discussion and Conclusions with labeling excerpts provided in **Appendix A**.

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The PMHS-MHT has reviewed the proposed afatinib labeling, and labeling recommendations are provided below.

MHT Summary of Labeling Comments and Recommendations

Highlights of Prescribing Information

The bullet point for fetal harm, under Warnings and Precautions was revised to “Embryo-Fetal Toxicity:”, to reference the section in the full prescribing information (FPI), to comply with requirement of current Safety Endpoints and Labeling Development Team (SEALD) labeling review tool. Language regarding embryo-fetal toxicity was revised to display preferred labeling language and to add information regarding contraception use during treatment with afatinib.

A “Use in Specific Populations” section was added to highlights, with bulleted language referencing the Nursing Mothers section of the FPI.

5 Warnings and Precautions

The title of section 5.7 was revised to “Embryo-Fetal Toxicity” to comply with requirements of the current SEALD labeling review tool. A summary statement was added to provide a concise description of risk.

Language regarding contraception for females of reproductive potential and to indicate when contact with the patient health care provider is needed was added. Appropriate labeling cross references were added. Language was revised to ensure use of appropriate regulatory language.

8 Use in Specific Populations

8.1 Pregnancy

The Pregnancy section was restructured and the sub-headings Risk Summary and Animal Data were added to provide an organized presentation of data.

8.3 Nursing Mothers

The Nursing Mothers section states that it is unknown whether afatinib is present in human milk, with appropriate regulatory language. Available data regarding the presence of afatinib in the milk of animals was revised.

8.6 Females and Males of Reproductive Potential

Information on pregnancy testing, contraception, and infertility that was located in other sections of labeling are now presented in the subsection, Females and Males of Reproductive Potential. Language regarding pregnancy planning and prevention counseling was added.

17 Patient Counseling Information

Language regarding pregnancy and lactation was revised to describe appropriate patient counseling, actions to mitigate the risk and provide instructions for contacting a health care provider.

Appendix A- PMHS-MHT Afatinib Labeling Recommendation Excerpts

Appendix A-PMHS-MHT Afatinib Labeling Recommendation Excerpts

Highlights of Prescribing Information

WARNINGS AND PRECAUTIONS
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use highly effective contraception. (5.7) (8.6)

USE IN SPECIFIC POPULATIONS
- Nursing Mothers: Discontinue drug or nursing. (8.3)

5 Warnings and Precautions

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, BRAND can cause fetal harm when administered to a pregnant woman. Afatinib was embryotoxic and abortifacient at late gestational stages in rabbits at doses of 5 mg/kg (approximately 0.2 times the human exposure at the recommended dose of 40 mg daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 2 weeks after the last dose of BRAND. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking BRAND *[see Use in Specific Populations (8.1) and (8.6)]*.

8 Use in Specific Populations- Pregnancy (8.1), Nursing Mothers (8.3), Females and Males of Reproductive Potential (8.6)

8.1 Pregnancy

Pregnancy Category D

Risk Summary
Based on its mechanism of action, BRAND can cause fetal harm when administered to a pregnant woman. Afatinib was embryotoxic and abortifacient at late gestational stages in rabbits at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Warnings and Precautions (5.7)].

Animal Data
Administration of aftatinib to pregnant rabbits at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC in humans at the recommended dose) or greater during the period of organogenesis caused maternal toxicity along with increased post-implantation

loss and abortion at late gestational stages. In the same study, at the high dose level of 10 mg/kg (approximately 0.7 times the exposure by AUC of the recommended human dose) there were reduced fetal weights, and increases in the incidence of runts, as well as visceral and dermal variations. In an embryofetal development study in rats there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg (approximately twice the exposure at the recommended human dose).

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Afatinib was present in the milk of lactating rats at concentrations 80-150 times higher than those found in plasma from 1 to 6 hours after administration. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from BRAND, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.6 Females and Males of Reproductive Potential

Contraception

Females
Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential to use highly effective contraception during treatment with BRAND, and for at least 2 weeks after the last dose of BRAND. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking BRAND [see Use in Specific Populations (8.1)]

17 Patient Counseling Information

- **Embryo-Fetal Toxicity**

  Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 2 weeks after taking the last dose of BRAND *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1),(8.6)]*.

- **Nursing Mothers**

  Advise patients to discontinue nursing while taking BRAND*[see Use in Specific Populations (8.3)]*.

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/s/

TAMMIE B BRENT HOWARD
05/13/2013

MELISSA S TASSINARI
05/13/2013

LYNNE P YAO
05/14/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 29, 2013

To: Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2 (DOP2)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **BRAND® (afatinib) Tablets, for oral use (afatinib)**
NDA# 201292
OPDP Review of Prescribing Information (PI), Medication Guide (MG) and carton/container labeling

---

In response to DOP2 November 21, 2012 consult request, OPDP has reviewed the proposed PI (FDA version sent via email to OPDP on April 15, 2013), MG [Division of Medical Policy Programs (DMPP)'s version on April 29, 2013] and carton/container labeling (version sent via email to OPDP on April 29, 2013) for afatinib.

Please see the attached PI with our comments incorporated therein. We agree with DMPP's comments on the MG and have no additional comment. In addition, OPDP does not have any comments for the carton/container labeling.

Thank you for the opportunity to provide comments on the proposed PI, MG and carton/container labeling for afatinib. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
04/29/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	April 29, 2013
To:	Patricia Keegan, M.D. Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (afatinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 201-292
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On November 15, 2012, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) 201-292 for TRADENAME (afatinib) tablets, with the proposed indication for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

On November 21, 2012, the Division of Oncology Products 2 (DOP2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (afatinib) tablets.

This review is written in response to a request by DOP2 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (afatinib) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (afatinib) tablets PPI received on November 15, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on April 15, 2013.
- Draft TRADENAME (afatinib) tablets Prescribing Information (PI) received on November 15, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on April 15, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
04/29/2013

BARBARA A FULLER
04/29/2013

LASHAWN M GRIFFITHS
04/29/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 16, 2013

TO: Deanne Varney, Regulatory Project Manager
Shakun Malik, M.D., Medical Officer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH**:** Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 201292
APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.
DRUG: Afatinib
NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION(S): Locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor inhibition (EGFR) mutation(s) as detected by an FDA-approved test.

CONSULTATION REQUEST DATE: December 8, 2012
INSPECTION SUMMARY GOAL DATE: April 19, 2013
DIVISION ACTION GOAL DATE: July 15, 2013
PDUFA DATE: July 15, 2013

I. BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc., [BI], seeks approval to market afatinib 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. EGFRs are expressed on the cell surface of a substantial percentage of NSCLCs. Binding of ligands to EGFRs on the cell surface leads to activation of multiple cellular signaling pathways, leading to effects such as increased proliferation and invasive ability, tumor angiogenesis, metastasis, and the ability of the cell to evade apoptosis.

Initial studies with first generation EGFR tyrosine kinase inhibitors, such as erlotinib (Tarceva), demonstrated a targeted biological activity in a subset of lung cancers; those with specific mutations within the EGFR-TKI domain. The efficacy of EGFR TKIs in NSCLC with EGFR mutations depends upon the type of genetic mutation. Apparent drug resistance occurs over time after the initiation of EGFR-TKI therapy. Molecular analysis of relapsed NSCLC samples reveals a compensatory mutation in the EGFR gene resulting in an amino acid alteration in the EGFR protein, thought to sterically hinder the access of reversible TKIs. Afatinib is a second generation, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), that covalently binds to and irreversibly blocks signaling from EGFRs.

The key study supporting this application is the pivotal Phase III study 1200.32 (LUX-Lung 3). This study was a randomized, open-label, active-controlled, parallel-group phase III trial designed to compare the efficacy and safety of afatinib monotherapy with pemetrexed/cisplatin chemotherapy as first-line treatment in EGFR TKI-naïve patients with Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung harboring an EGFR mutation. Eligible subjects were randomized in a 2:1 ratio to receive afatinib or pemetrexed/cisplatin chemotherapy. Due to the inherent differences between the two treatment arms (patients randomized to the afatinib arm received oral tablets while patients randomized to the chemotherapy arm received an intravenous infusion), the trial was open-label.

The planned sample size for this study was 330 subjects (220 in the afatinib arm and 110 in the pemetrexed/cisplatin arm). A total of 1269 subjects were screened, 230 were entered into the afatinib arm, and 115 were entered into the pemetrexed/cisplatin arm. The study was conducted at approximately 133 centers in 25 countries in Asia, Australia, Europe, North America, and South America. This study was conducted under IND.

Three clinical sites, chosen on the basis of patient number enrolled at each site were inspected for this NDA. Because this is a new molecular entity, the sponsor and a CRO (Independent Review Committee [IRC] for progression free survival [PFS] determination) were also inspected.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Sarayut Lucien Geater, MD Songklanagarind Hospital, Department of Medicine Respiratory and Respiratory Critical Care Medicine Division 15 Kanjanawanich Road Hat Yai Songkhla 90110, Thailand	Protocol: 1200.32 (LUX-Lung 3) Site #: 3701 Number of Subjects: 33	March 4-6, 2013	Pending Interim classification: NAI
CI#2: Prof. Chih-Hsin Yang National Taiwan University Hospital Dept. of Oncology, 7, Chung–Shan South Road, Taipei City, 10002, Taiwan	Protocol: 1200.32 (LUX-Lung 3) Site #: 3601 Number of Subjects: 12	March 11-12, 2013	Pending Interim classification: NAI
CI#3: Prof. Dr. med. Martin Schuler Universitätsklinikum Essen Westdeutsches Tumorzentrum Innere Klinik und Poliklinik Hufelandstraße 55 45122 Essen, Germany	Protocol: 1200.32 (LUX-Lung 3) Site #: 4305 Number of Subjects: 10	March 18-22, 2013	Pending Interim classification: VAI
CRO#1: (b) (4) (b) (4)	Protocol: 1200.32 (LUX-Lung 3) Site#: 3601 (Yang) 3701 (Geater) 4305 (Schuler) 3304 (Lee) 4806 (Collinson) 5504 (Orlov) Subjects Records Reviewed: 64	March 25-28, 2013	Pending Interim classification: NAI
Sponsor: Boehringer Ingelheim Pharmaceuticals Inc 900 Ridgebury Road Ridgefield, CT 06877	Protocol: 1200.32 (LUX-Lung 3) Site#: 3601 (Yang) 3701 (Geater) 4305 (Schuler) Subjects Records Reviewed: 55	March 25-28, 2013	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CI#1: – Sarayut Lucien Geater, MD**
   Songklanagarind Hospital
   Department of Medicine
   Respiratory and Respiratory Critical Care Medicine Division
   15 Kanjanawanich Road
   Hat Yai Songkhla 90110, Thailand

   a. **What was inspected:** The site screened 98 subjects, and 33 subjects were enrolled and randomized. Of these 33 subjects, 25 completed the study, 3 withdrew consent and 5 withdrew due to AEs or death. The study records of all 33 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring and safety reports, and financial disclosure forms.

   b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data, as determined by the CI, for the subjects enrolled at this site were verified. There was no evidence of under-reporting of AEs. Test article accountability was confirmed, Ethics Committee approvals were appropriately obtained, and all 33 subjects appropriately signed informed consent documents. No Form FDA 483 was issued.

   c. **Assessment of data integrity:** The data for Dr. Geater's site, associated with Study 1200.32 (LUX-Lung 3) submitted to the Agency in support of NDA 201292, appear reliable based on available information.

   Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. **CI#2: – Prof. Chih-Hsin Yang**
   National Taiwan University Hospital
   Dept. of Oncology, 7,
   Chung−Shan South Road,
   Taipei City, 10002, Taiwan

a. **What was inspected:** The site screened 28 subjects, and 12 subjects were enrolled and randomized. Of these 12 subjects, 10 completed the study, 1 withdrew consent, and 1 withdrew due to AE. The study records of all 12 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring and safety reports, and financial disclosure forms.

b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data, as determined by the CI, for the subjects enrolled at this site were verified. There was no evidence of under-reporting of AEs. Study records were complete and organized. Test article accountability was confirmed, Ethics Committee approvals were appropriately obtained, and all 12 subjects appropriately signed informed consent documents. No Form FDA 483 was issued.

c. **Assessment of data integrity:** The data for Dr. Yang's site, associated with Study 1200.32 (LUX-Lung 3), submitted to the Agency in support of NDA 201292, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. **CI#3: – Prof. Dr. med. Martin Schuler**
   Universitätsklinikum Essen
   Westdeutsches
   Tumorzentrum
   Innere Klinik und Poliklinik
   Hufelandstraße 55
   45122 Essen, Germany

a. **What was inspected:** The site screened 42 subjects, and 10 subjects were enrolled and randomized. All 10 subjects completed the study. The study records of all 10 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included

comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, including EGFR results for all screen-failures, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring and safety reports, and financial disclosure forms.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data, as determined by the CI, for the subjects enrolled at this site were verified. There was no evidence of under-reporting of AEs. The FDA field investigator observed that two subjects did not sign updated informed consent in a timely fashion, several sub-investigators were either late with or had no financial disclosure documentation generated, and there was no documentation of study-specific training for some study site staff. The FDA field investigator issued a Form FDA 483 for the following violations:

1. Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative, and the situation did not meet the criteria in 21 CFR 50.23 - 50.24 for exception. Specifically, the following subjects were not reconsented during the study trial when an updated informed consent version was approved for the study:

    a. Subject 4305037 did not sign the Informed Consent Version 4.0, dated July 20, 2010, until August 23, 2012, or the Informed Consent Version 5.0, dated February 2, 2011, until August 23, 2012.
    b. Subject 4305041 did not sign the Informed Consent Version 5.0, dated February 2, 2011, until December 8, 2011.

2. Information necessary for submission of required financial disclosure statements to FDA was not provided to the sponsor. Specifically,

    a. Sub-Investigator (b) (6) did not submit a financial disclosure statement.
    b. The following Sub-Investigators did not submit financial disclosure statements at the initiation of the study:
        i. Sub-Investigator (b) (6) started with the study on April 20, 2010, yet did not submit a financial disclosure until February 5, 2013.
        ii. Sub-Investigator (b) (6) started with the study on April 20, 2010, yet did not submit a financial disclosure until January 29, 2013.
        iii. Sub-Investigator (b) (6) started with the study on November 2, 2009, yet did not submit a financial disclosure until August 30, 2010.

c. Sub-Investigator (b) (6) did not fully complete the financial disclosure form in that she did not mark 'Yes' or 'No' regarding financial interests in the test product or licensing agreement.

3. An investigation was not conducted in accordance with the investigational plan. Specifically, for eight study site staff, there is no documentation to show that study-specific training was provided.

OSI Reviewer Notes: *According to the FDA field investigator, the site appeared to conduct the study very well. While some sub-investigators lacked certain documentation to demonstrate study-specific training, the staff was conducting the study consistent with the protocol. These observations should not importantly impact data generated by this site.*

c. Assessment of data integrity: Not withstanding the observations noted above, the data for Dr. Schuler's site, associated with Study 1200.32 (LUX-Lung 3) submitted to the Agency in support of NDA 201292, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. CRO: (b) (4)
(b) (4)

a. What was inspected: The CRO [IRC] was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection included a review of the firm's organization, charters, contracts, study plans, system validation records, standard operating procedures, oncology and radiology analysis forms, and subject overall endpoints. Efficacy endpoints generated by this CRO were compared to data listings submitted to the application (tumor measurements and disease progression). All of the primary efficacy endpoints were reviewed for all applicable subjects at each of the 6 clinical sites noted in the table (Section II. RESULTS [by site]) above for the identified study inspected at this CRO site.

b. General observations/commentary: Records and procedures were adequate, and generally well organized. The primary efficacy endpoint data generated by this IRC and submitted to NDA 201292 were verifiable for the 6 clinical sites referred to above, which is a total of 64 subjects' endpoints. There were no discrepancies. Also, there was no evidence of IRC non-compliance with the Charter. No Form FDA 483 was issued.

c. Assessment of data integrity: The data generated at this site, as it pertains to Study 1200.32 (LUX-Lung 3) were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The data from this CRO submitted to the Agency in support of NDA 201292 appear reliable.

Note: Observations noted for this CRO are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

5. Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Ridgefield, CT 06877

a. What was inspected: The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection covered adherence to protocol, and review of the firm's SOPs, monitoring reports, actions related to monitoring deficiencies, Ethics Committee/IRB approvals, completed Form FDA 1572s, communications with the sites, drug accountability and review of data management from the clinical study sites to the submission of the NDA to the Agency. The FDA field investigator specifically audited subject records from 3 clinical study sites; Site 3601 (Dr. Yang, 12 subjects), Site 3701 (Dr. Geater; 33 subjects), and Site 4305 (Dr. Schuler; 10 subjects), as well as limited record samples from other clinical sites for the study. The FDA field investigator also audited 34 out of 345 IVRS records for accuracy of randomization documentation.

b. General observations/commentary: Records and procedures were clear, and generally well organized. Regarding subject disposition for the overall study, there were 1269 subjects screened, 345 randomized, 340 treated with test article, and 60 that completed 6 courses of therapy. At the time of data analysis cut-off (March 6, 2013) there were 32 subjects still on treatment. There was nothing to indicate under-reporting of AEs/SAEs. There was no evidence of under-reporting of protocol violations. There was no evidence that subjects received treatment other than that assigned by the IVRS. Overall site monitoring appeared adequate. Monitoring reports indicated that efforts were made by the Sponsor to ensure site compliance with the protocol. The Sponsor appeared to maintain adequate oversight of the study. No Form FDA 483 was issued.

c. Assessment of data integrity: The data generated at this site, as it pertains to Study 1200.32 (LUX-Lung 3) were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this Sponsor submitted to the Agency in support of NDA 201292 appear reliable.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators, Dr. Yang, Dr. Geater and Dr. Schuler, the study sponsor, Boehringer Ingelheim Pharmaceuticals, Inc., and CRO (b) (4)., the study data collected appear reliable.

The clinical site of Dr. Schuler (Site 4305) was issued a Form FDA 483 citing inspectional observations and the preliminary classification for this inspection is Voluntary Action Indicated (VAI). The preliminary classifications for the remaining inspections of Dr. Yang, Dr. Geater, the sponsor [BI], and the CRO [IRC (b) (4) (b) (4)] are No Action Indicated (NAI).

The three inspected clinical sites revealed nothing to indicate under-reporting of AEs/SAEs. In addition, the primary efficacy endpoint data generated by the CRO were verifiable for the three clinical sites inspected and three additional randomly selected clinical sites (#3304, #4806, and #5504); a total of 64 subjects' endpoints were verified.

The inspection of Dr. Schuler's site (4305) found that there were a few protocol deviations in that subjects were not always reconsented in a timely fashion when an updated informed consent version was approved for the study, that several sub-investigators were either late or had no financial disclosure documentation generated, and that there was no documentation of study-specific training for some study site staff. According to the FDA field investigator, the site appeared to conduct the study very well. Although some sub-investigators lacked certain documentation to demonstrate study-specific training, the staff was conducting the study consistent with the protocol. Overall these inspectional observations for Dr. Schuler's site (4305) should not importantly impact data generated by this site.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data for Study 1200.32 (LUX-Lung 3) in support of this application may be considered reliable based on available information.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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/s/

LAUREN C IACONO-CONNORS
04/16/2013

JANICE K POHLMAN
04/16/2013

SUSAN D THOMPSON
04/17/2013

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

Label, Labeling and Packaging Review

Date:	April 9, 2013
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Gilotrif (Afatinib) Tablets, 20 mg, 30 mg, 40 mg (b) (4)
Application Type/Number:	NDA 201292
Applicant:	Boehringer Ingelheim
OSE RCM #:	2012-2800

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container labels, carton, and insert labeling for Gilotrif (Afatinib), NDA 201292, for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the November 26, 2012 proprietary name submission.

- Active Ingredient: Afatinib
- Indication of Use: For the treatment of patients with locally advanced or metastatic non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) mutations.
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 20 mg, 30 mg, 40 mg (b) (4)
- Dose and Frequency: Forty mg (40 mg) orally once daily for first-line treatment or for patients not previously treated with an EGFR-tyrosine kinase inhibitor (EGFR-TKI naïve patients) (b) (4)
- How Supplied: 30 count bottles for all strengths
- Storage: Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F). Protect from exposure to high humidity.
- Container and Closure System: The container closure system is a (b) (4) plastic bottle, closed with a (b) (4) screw cap (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted November 14, 2012 (Appendix A)
- Carton Labeling submitted November 14, 2012 (Appendix B)
- Inlyta (Axitinib) Container Labels from the Daily Med website as of February 1, 2013 (Appendix C)
- Insert Labeling submitted November 14, 2012

3 RESULTS

3.1 LABELS AND LABELING

DMEPA notes that the QR (Quick Response) code and the graphic immediately to the right of the brand and established names on the container labels distract from other important information and, therefore, should be decreased in prominence. Also, the statement "30 tablets" on the top and side panels of the carton labeling should be moved away from the strength to prevent confusion.

We also note the three block color graphic located on the principal display panel of the container labels and carton labeling has the same colors that are used for the 20 mg and 40 mg product strength differentiation.

Because the established names, axitinib and afatinib, are orthographically and phonetically similar (see section 4 of this review) and both products may be stored near each other on the pharmacy shelf, we reviewed the labels for Inlyta (axitinib) to ensure that they are well differentiated from the proposed labels and labeling of Afatinib in order to mitigate wrong product selection errors. We note that the color used for the strength presentation of the 40 mg afatinib product is similar to the color used for the strength differentiation of the currently marketed 5 mg Inlyta (Axitinib) product – see Appendix C.

(b) (4)

4 DISCUSSION

4.1 ESTABLISHED NAME SIMILARITY

In a teleconference on May 23, 2012, DMEPA asked the Applicant to change the established name, Afatinib, for this product because it was similar to the established name, Axitinib (Inlyta). The Applicant's name (Afatinib) is a publicly registered USAN name.

In correspondence dated October 1, 2012, the Applicant indicated that they concluded that an alternate USAN or INN should not be requested. The FDA USAN liaison member or the Applicant did not pursue or initiate other options to minimize the potential for name confusion.

DMEPA considered tall man lettering, but the Applicant of Inlyta (Axitinib) would be required to change their labels and labeling, a significant burden to the Inlyta Applicant, without any evidence of name confusion. This would also create complicated negotiations between two parties from a confidentiality perspective since Inlyta (Axitinib) is currently FDA approved and Afatinib is not FDA approved.

Additionally, the composition of the two names do not provide for adequate differentiation when tall man lettering is used. For example, the letter 'A' in the first position would be capitalized for both names. The letters in the second and third position of each name are the only letters that are different between the names. Therefore, the letters in the second and third position of each name could be the only letters that can be used for tall man lettering. Thus, in a tall man letter scenario both names would start with a capital letter 'A' and have tall man lettering in the second and third position slightly taller than the capital letter 'A' (AFAtinib vs. AXItinib). This may not result in adequate differentiation between established names.

Because hospitals use established names more frequently, this practice setting is more likely to see selection errors due to similarities between the established names. Also, if generics are introduced to the marketplace in the future, various techniques will need to be implemented to try to differentiate the products. This may be especially problematic and difficult to implement on unit dose packaging because of the size of the packaging.

Because of these established name concerns, DMEPA has included a recommendation in section 5 of this review to help ensure that the labels and labeling between axitinib and afatinib are well differentiated. Additionally, if Afatinib is FDA approved, DMEPA will monitor for errors post-approval due to the similarity of the established names Afatinib and Axitinib.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

5.1 COMMENTS TO THE DIVISION

A. Highlights of Prescribing Information, Dosage and Administration

B. Recommended Dose, Section 2.1

C. Instructions for Taking BRAND, Section 17.5

(b) (4)

D. Patient Information, "How Should I take BRAND?"

(b) (4)

E. Patient Information, "How should I store BRAND?"

1. Add the statement "Do not place medication in daily or weekly pill boxes" to the end of the second bullet point.

5.2 COMMENTS TO THE APPLICANT

A. Container Labels and Carton Labeling

1. The colors used to highlight and differentiate the 20 mg and 40 mg strength presentations are similar to the colors used for the three block color graphic on the principal display panel for all strengths. Because color is used to differentiate strength, using a similar color for the 20 mg and 40 mg strength that is also used to create a three block color graphic on the principal display panel may result in wrong product strength selection errors. Select a color for the 20 mg and 40 mg strength presentations that is not similar to the colors incorporated into the three block color graphic. Or, delete the three block color graphic or select different colors for the three block color graphic.
2. The color used for the strength presentation of the 40 mg afatinib product is very similar to the color used for the strength presentation of the currently marketed 5 mg Inlyta (Axitinib) product. Because the established names, axitinib and afatinib, are orthographically and phonetically similar and both products may be stored near each other on the pharmacy shelf, it is important to differentiate these products with different colors to mitigate the risk of wrong product selection. Select a color for the 40 mg afatinib strength presentation that is different than the color used for the strength presentation of the currently marketed 5 mg Inlyta (axitinib) product.
3. Delete or decrease the prominence of the graphic next to the proprietary and established names because it competes with other important information. If the graphic is decreased in prominence, then ensure there is sufficient white space between the proprietary and established names and the graphic.
4. Revise the statement (b) (4) to read "Attention: Dispense and Store Medication in the Original Container to Protect from Light and Humidity".

The revised statement will provide information for the pharmacist and patient. If space constraints do not permit the entire statement, then consider deleting the rationale, "to Protect from Light and Humidity".

5. Ensure the established name is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printer features per 21 CFR 201.10(g)(2). Consider revising the established name to appear in a black color with a bolded font.
6. Un-bold the statement "30 tablets" wherever it occurs.

B. Container Label

1. The Quick Response (QR) code is too prominent and competes with the strength statement and other important information. Decrease the size of the QR code.

C. Carton Labeling

1. Move the statement "30 tablets" on the top and side panels away from the strength presentation. Post marketing data shows that confusion with the strength and bottle count can occur when they are in close proximity with each other.

If you have questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES H SCHLICK
04/09/2013

TODD D BRIDGES
04/09/2013

SCOTT M DALLAS
04/09/2013

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 27, 2013

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Deanne Varney, DOP2

Subject: QT-IRT Consult to NDA 201292

This memo responds to your consult to us dated December 3, 2012 regarding proposed labeling of afatinib. The QT-IRT received and reviewed the following materials:

- Your Consult
- IRT Review of Study 1200.24 under IND 67969 (July 2, 2012)

QT-IRT Comments for DOP2

IRT previously reviewed a dedicated QT study for afatinib (Study 1200.24) on July 2, 2012. No large changes (i.e., > 20 ms) in QTc interval were detected in the study. Below, we provide our proposed labeling language based on our review. Our labeling recommendations are suggestions only. We defer final labeling to the Division.

12.6 Cardiac Electrophysiology

The effect of multiple doses of BRAND (50 mg once daily) on the QTc interval was evaluated in an open label, single arm study in patients with relapsed or refractory solid tumors. No large changes in the mean QTc interval (i.e., > 20 ms) were detected in the study.

Thank you for requesting our input into the development of this product under NDA 201292. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

KEVIN M KRUDYS
03/27/2013

NORMAN L STOCKBRIDGE
03/27/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 201292

Application Type: NME NDA, Type 1

Name of Drug: Afatinib tablets (20, 30, 40 (b) (4) mg)

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Submission Date: November 14, 2012

Receipt Date: November 15, 2012

1.0 Regulatory History and Applicant's Main Proposals

This application proposes afatinib as a treatment for 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. The clinical development of afatinib occurred under INDs 67969 and 114002.

An EOP2 meeting was held on March 1, 2011 and a pre-NDA meeting was held on December 9, 2011. A follow-up pre-NDA meeting was held on October 10, 2012 in order to discuss PDUFA V requirements.

A carcinogenicity SPA was agreed to on March 29, 2012.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 4, 2013. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *The HL exceeds one-half page. The applicant has requested a waiver of the half-page requirement.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

Selected Requirements of Prescribing Information (SRPI)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Selected Requirements of Prescribing Information (SRPI)

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Currently states only "See FDA-approved patient labeling". Needs to state "See FDA-approved patient labeling (Patient Information)"*

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

/s/

DEANNE R VARNEY
12/27/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 201292 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Thundrion (pending) Established/Proper Name: Afatinib Dosage Form: Tablet Strengths: 20, 30, 40, (b) (4) mg		
Applicant: Boehringer Ingelheim Agent for Applicant (if applicable): N/A		
Date of Application: 11/14/2012 Date of Receipt: 11/15/2012 Date clock started after UN:		
PDUFA Goal Date: 7/15/2013	Action Goal Date (if different):	
Filing Date: 1/14/2013	Date of Filing Meeting: 12/13/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : 1		
Proposed indication(s)/Proposed change(s): 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		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 67969 and 114002	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		✓		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		✓		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		✓		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			✓	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	✓			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			✓	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	✓			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		✓		
• If yes, were all of them submitted on time?			✓	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	✓			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	✓			
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	✓			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	✓			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			✓	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	✓			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		✓		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	✓			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			✓	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		✓		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	✓			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		✓		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	✓			
Is the PI submitted in PLR format?[4]	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	✓			QT-IRT: 12/3/12 SEALD: 11/21/12 Patient Labeling: 11/21/12 Maternal Health: 11/21/12
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 3/1/2011 ***If yes, distribute minutes before filing meeting***	✓			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 12/9/2011 and 10/10/2012 ***If yes, distribute minutes before filing meeting***	✓			
Any Special Protocol Assessments (SPAs)? **Date(s):** 3/29/12 ***If yes, distribute letter and/or relevant minutes before filing meeting***	✓			Carcinogenicity

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 13, 2012

BLA/NDA/Supp #: 201292

PROPRIETARY NAME: Thundrion (proposed)

ESTABLISHED/PROPER NAME: Afatinib

DOSAGE FORM/STRENGTH: Tablet - 20, 30, 40 (b) (4) mg

APPLICANT: Boehringer Ingelheim

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): 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

BACKGROUND: This is a new NDA for NSCLC. An EOP2 meeting was held on March 1, 2011 and a pre-NDA meeting was held on December 9, 2011. A follow-up pre-NDA meeting was held on October 10, 2012 in order to discuss PDUFA V requirements. A carcinogenicity SPA was agreed to on March 29, 2012.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Deanne Varney	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Anthony Murgo		Y
Clinical	Reviewer:	Shakun Malik	Y
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Jun Yang and Runyan Jin	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Jonathan Norton	Y
	TL:	Kun He	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dubravka Kufrin	Y
	TL:	Whitney Helms	Y
Product Quality (CMC)	Reviewer:	Li Shan Hsieh	Y
	TL:	Liang Zhou Nallaperum Chidambaram	Y
Facility Review/Inspection	Reviewer:	Mahesh Ramandhan (TL)	Y
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	Y
	TL:	Todd Bridges	N
OSE/DRISK/DPV/DEPI	Reviewer:	Bob Pratt, DRISK Kate Coyle, DPV Adel Abou-Ali, DEPI	N Y N
	TL:	Cynthia Lacivita, DRISK TL Corrinne Kulick, DPV TL	N

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connors	N
	TL:	Janice Pohlman	N
Other reviewers	Carol Broadnax, OPDP Professional Karen Munoz, OPDP Consumer Tammy Brent-Howard, Maternal Health Karen Dowdy, PLT		N N N N
Other attendees	Nina Hunter, CDRH Rick Pazdur, Office Director Jeff Summers, DDS Debasis Ghosh, CMC		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

• Electronic Submission comments **List comments**: No comments	☐ Not Applicable
CLINICAL **Comments**: No issues identified. An IR was sent requesting BI to identify where in the submission the rationale for assuming the applicability of foreign data is provided.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ NO ☒ To be determined Reason: The need for an AC will be determined after review of the data provided in the 120-day safety update.
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: No filing issues identified. A complete clinical pharmacology package was provided.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: No filing issues identified.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: No filing issues identified.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: No filing issues identified.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: A recent inspection of the following site lead to potential OAI status: Boehringer Ingelheim Pharma GmbH & Co. KG FEI: 3002806556	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: None at this time.	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, M.D. **Date of Mid-Cycle Meeting** : February 7, 2012 **21st Century Review Milestones:** Filing Action: January 14, 2013 74-Day Letter: January 28, 2013 Midcycle Communication: February 28, 2013 Late Cycle Meeting: May 5, 2013 Final Action: July 15, 2013	

Comments: The following was discussed during the filing meeting: 1. The review team agreed to review this submission as a priority review (8 month clock). 3. The PeRC meeting to discuss the full pediatric waiver was scheduled for March 27, 2013. 4. Standing monthly meetings were set up from January – July 2013. 5. Labeling meetings have been scheduled for March and April 2013. 6. Clinical sites have been selected for inspections, inspections are being scheduled.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the

	completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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

/s/

DEANNE R VARNEY
12/20/2012