

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208772Orig1s000

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

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208772
PDUFA Goal Date	April 29, 2017
OSE RCM #	2016 – 1961 2016 – 1963
Reviewer Name(s)	Elizabeth Everhart, MSN, RN, ACNP
Team Leader	Naomi Redd, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	January 30, 2017; Addendum March 27, 2017
Subject	Evaluation of Need for a REMS
Established Name	Brigatinib
Trade Name	Alunbrig (proposed)
Name of Applicant	Ariad Pharmaceuticals
Therapeutic Class	Anaplastic lymphoma kinase (ALK) receptor tyrosine kinase inhibitor
Formulation(s)	30 mg and 60 mg tablets
Dosing Regimen	Starting dose of 90 mg orally once daily for the first seven days, then 180 mg orally once daily

1 EXECUTIVE SUMMARY AND ADDENDUM

This is an addendum to the review¹ by the Division of Risk Management (DRISK) that evaluated whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Alunbrig (brigatinib) is necessary to ensure the benefits of this product outweigh its risks. Ariad submitted a New Drug Application (NDA 208772) for brigatinib with the proposed indication of the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The applicant did not submit a REMS with this application but proposed communicating the serious risks of pulmonary adverse reactions, hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevations, and embryo-fetal toxicity in the Warnings and Precautions section of the label, including recommendations for dose modifications to mitigate those serious risks.

Since completion of the DRISK review in January, 2017, DOP I added language to communicate the risk of hyperglycemia to the Warnings and Precautions section of the label. During the clinical review, CTCAE^a grade 3 hyperglycemia, based on laboratory assessment of fasting serum glucose levels, was noted to have occurred in 4% of patients treated with brigatinib in Study 1. Additionally, 2 of 20 patients with known diabetes or glucose intolerance at baseline required the initiation of insulin while being treated with brigatinib. The label will further recommend monitoring fasting serum glucose prior to and during treatment with brigatinib, as well as potential dose reductions/discontinuation as appropriate.²

The addition of the risk of hyperglycemia does not change DRISK's recommendation that a REMS is not necessary to assure that the benefits of brigatinib outweigh its risks. Metastatic ALK + NSCLC is a serious medical condition with very poor survival and healthcare providers, typically medical oncologists, who treat metastatic ALK + NSCLC, should be familiar with the risks associated with ALK inhibitors, including the importance of patient monitoring.

DRISK and the Division of Oncology Products (DOP) II agree that a REMS is not necessary to ensure the benefits of brigatinib outweigh its risks.

2 REFERENCES

¹ Everhart, Elizabeth. Evaluation for need for a REMS Review for Brigatinib, NDA 208772, submitted to DARRTS on January 30, 2017

² Ariad. Brigatinib draft label, March, 2017

^a NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Alunbrig (brigatinib) is necessary to ensure the benefits of this product outweigh its risks. Ariad submitted a New Drug Application (NDA 208772) for brigatinib with the proposed indication of the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The applicant did not submit a REMS with this application but proposed communicating the serious risks of pulmonary adverse reactions, hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevations, and embryo-fetal toxicity in the Warnings and Precautions section of the label, including recommendations for dose modifications to mitigate those serious risks.

DRISK and the Division of Oncology Products (DOP) II agree that a REMS is not necessary to ensure the benefits of brigatinib outweigh its risks. Three other ALK inhibitors with similar risks, crizotinib (accelerated approval 2011, full approval 2013), ceritinib, (accelerated approval in 2014) and alectinib (accelerated approval in 2015) are all approved without REMS. Those risks include: pulmonary adverse events (pneumonitis and interstitial lung disease (ILD)), bradycardia, vision impairment, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation, and embryo fetal toxicity seen in animal studies. If approved, similar to crizotinib, ceritinib, and, alectinib, the brigatinib product labeling will not include a boxed warning.

Metastatic ALK + NSCLC is a serious medical condition with very poor survival and healthcare providers, typically medical oncologists, who treat metastatic ALK + NSCLC, should be familiar with the risks associated with ALK inhibitors, including the importance of patient monitoring.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Alunbrig (brigatinib) is necessary to ensure the benefits of this product outweigh its risks. Ariad submitted a New Drug Application (NDA 208772) for brigatinib with the proposed indication of the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This application is under review in the Division of Oncology Products II (DOP II). The applicant did not submit a REMS, but proposes communicating the serious risks of pulmonary adverse reactions (pneumonitis and interstitial lung disease (ILD), hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevations, and embryo-fetal toxicity in the Warnings and Precautions section of the label including recommendations for patient monitoring and dose modifications to mitigate those risks.

2 Background

2.1 PRODUCT INFORMATION

Brigatinib, a NME^a, is a tyrosine kinase inhibitor (TKI) that targets the receptor for anaplastic lymphoma kinase (ALK). Brigatinib is a pan ALK inhibitor and in preclinical studies it was shown to have retained activity against all clinically relevant ALK inhibitor (crizotinib, ceritinib, and alectinib) resistant mutants identified to date.¹

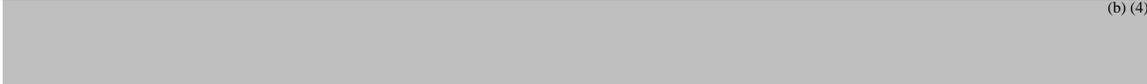
Brigatinib's indication is for use in the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. The applicant was granted breakthrough therapy designation, as well as rolling review, and orphan drug designation. The applicant is seeking accelerated approval based on tumor response rate and duration of response.

Brigatinib is a small molecule TKI supplied in 30 mg and 90 mg tablets to be administered at a starting doses of 90 mg orally once daily for the first seven days, and then 180 mg orally once daily until disease progression or unacceptable toxicity.^b If a dose reduction is required while a patient is on the 90 mg starting dose, the dose reduction level is to 60 mg, if a second dose reduction is required, the drug should be permanently discontinued. If a dose reduction is required while a patient is receiving 180 mg daily, the first dose reduction is to 120 mg, the second dose reduction is to 90 mg, and the third dose reduction is to 60 mg. If patients are unable to tolerate 60 mg, the drug should be permanently discontinued. The Prescribing Information (PI) for brigatinib includes a table describing recommended dose reductions for the serious adverse events of pneumonitis, bradycardia, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation events, as well as any other NCI CTCAE^c grade 3 or 4 adverse event.

Brigatinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208772 relevant to this review:

-  (b) (4)
- 10/01/2014: Breakthrough designation request granted for brigatinib for the treatment of patients with ALK-positive NSCLC whose tumors are resistant to crizotinib.
- 09/08/2015: A thorough QT Study Review conducted under IND 110935 evaluating clinical trial AP26113-11-101. No large changes in the QTcF interval were detected at the potential therapeutic doses. The study did not include placebo and positive control (moxifloxacin) arms; therefore, no assay sensitivity was established.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

^c National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0.

- 04/15/2016: Type B, Pre-NDA meeting. Applicant informed at pre-NDA meeting that a REMS for brigatinib was not needed for FDA to file the application.
- 06/16/2016: NDA 208772 Part 1 of 3 rolling submission for received treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
- 07/28/2016: NDA 208772 Part 2 of 3 rolling submission received.
- 08/30/16: NDA 208772 Part 3 of 3 rolling submission received, as well as a request for Priority Review designation.
- 09/30/16: Clinical Filing review completed; no filing issues identified.
- 12/14/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for brigatinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Lung cancer is the leading cause of cancer-related death in the United States (U.S.) in both men and women, as well as the second most commonly diagnosed cancer in both sexes. In the U.S. in 2016, approximately 224,400 people will be diagnosed and an estimated 158,000 deaths are expected to occur as a result of lung cancer. The 1- and 5- year survival rates for lung cancer are 44% and 17%, respectively. If a lung cancer is detected in a localized stage, the 5-year survival is 55%; however, only 16% of patients present in a localized stage.² For patients with metastatic lung cancer, the 5-year survival rate is less than 5%.^d

Lung cancer is divided histologically into small cell (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of all lung cancers. Generally, as a class, NSCLC is insensitive to chemotherapy and radiation therapy as compared SCLC. Of the patients with NSCLC, only approximately 2%-7% are found to have the ALK molecular abnormality in their tumors. This represents approximately 7,000 to 25,000 patients in the U.S.^{e, 3,4}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

In the U.S., crizotinib received accelerated approval in 2011 for the treatment of advanced ALK+ NSCLC and full approval in 2013. However, nearly all patients with ALK+ NSCLC develop resistance to crizotinib and progress on treatment, often with brain metastases. Two other ALK inhibitors, ceritinib (granted accelerated approval in 2014) and alectinib (granted accelerated approval in 2015), have been approved

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^e Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

for patients who progress on, or are intolerant to, crizotinib. While these medications have been shown to be effective in patients with crizotinib resistance, they also have been shown to have ALK secondary mutations that lead to treatment resistance, often within the first year of treatment. Chemotherapy agents docetaxel or pemetrexed are both approved as second-line treatments for ALK+ NSCLC following platinum-based chemotherapy.

Quality of life and life expectancy in NSCLC patients with brain metastases is quite diminished; therefore, there is an ongoing medical need for an ALK inhibitor that is effective against CNS/brain metastases and active against ALK mutations that confer resistance to the other approved treatments for ALK+ NSCLC.

4 Benefit Assessment^f

The following information is summarized from the review designation memo of Dr. Donoghue, acting associate director in the Division of Oncology Products II⁵ and the Midcycle Clinical and Statistical review slides.⁶

Pivotal study AP26113-13-201 (Study 1) is a randomized phase 2 study of brigatinib in patients with ALK+ NSCLC previously treated with crizotinib. The primary objectives of the study were determinations of the efficacy by overall response rate (ORR) and safety of brigatinib in patients with ALK+ locally advanced or metastatic NSCLC whose disease had progressed on crizotinib. The primary efficacy endpoint was investigator-assessed confirmed ORR by RECIST v1.1^g; a total of 222 patients were enrolled. The study includes two dose arms: Arm A is 90 mg daily, Arm B is 90 mg daily for seven days and then 180 mg daily thereafter. The study's first patient was dosed in June, 2014 and the last patient's first dose was September, 2015. The study is ongoing; as of the data extraction date of February 29, 2016, 140 patients remain on study treatment.

In Study 1, the ORR (95% CI) according to IRC (Independent Review Committee) assessment was 48.2% (54/112) in the 90 mg QD arm and 52.7% (58/110) in the 180 mg QD arm. The median (95% CI) duration of response (DoR) according to IRC assessment was 13.8 months (7.4 – NE) in the 90 mg QD arm and 13.8 months (9 – NE) in the 180 mg QD arm. Regarding brain metastases, in patients with measurable brain metastases, the confirmed intracranial ORR was 42.3% (11/26) of patients in Arm A and 66.7% (12/18) of patients in Arm B for patients with IRC-assessed measurable brain metastases at baseline. In patients with only non-measurable brain metastases, intracranial CR was observed in 7.4% (4/54) of patients in Arm A and 18.2% (10/55) of patients in Arm B. Intracranial CR in this study was defined as complete radiographic disappearance of non-measurable lesions and it was the only response possible for patients with non-measurable lesions.

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

^g Response Evaluation Criteria in Solid Tumors, version 1.1

5 Risk Assessment^h & Safe-Use Conditions

An overview of the adverse events of special interest is provided herein. As discussed by the medical officer, Dr. Horiba, at the mid-cycle meeting, there were 18 fatal adverse events in Arm A of study AP26113-13-201 (Study 1), of which 13 were considered disease progression; in Arm B of the same study, there were 8 deaths, 5 of which were considered disease progression.⁷

The risks associated with brigatinib are similar to the other approved TKIs for ALK+ NSCLC, including: pulmonary adverse events (pneumonitis and interstitial lung disease (ILD)), bradycardia, vision impairment, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevation, and embryo-fetal toxicity seen in animal studies. These risks will be described in the Warnings and Precautions section of the PI and, aside from embryo-fetal toxicity, will include recommendations for monitoring and dose reductions based upon severity.

Two other risks of special interest seen in clinical studies of brigatinib, but not with other TKIs approved for ALK+ NSCLC, are hypertension and an early onset of pulmonary events (EOPE), which is characterized by dyspnea, hypoxia, cough, pneumonia, and pneumonitis observed early after initiation of brigatinib in some patients; these adverse events of special interest are discussed in the subsections below.⁸

Hypertension is a risk associated with, and described in the Warnings and Precautions section of the PIs of some TKIs approved for other conditions, including axitinib⁹, approved for renal cell carcinoma (RCC) and cabozantinib¹⁰, approved for RCC and medullary thyroid cancer.

5.1 PULMONARY ADVERSE REACTIONS

In clinical trials, brigatinib was associated with pulmonary adverse reactions, both EOPE and pneumonitis and ILD. All currently approved ALK inhibitors and several epidermal growth factor receptor (EGFR) inhibitors used to treat metastatic NSCLC are also associated with pneumonitis and ILD, but not with the early onset pulmonary events seen with brigatinib. The EOPE were characterized the manifestation of symptoms including dyspnea, cough, pneumonia, hypoxia, and pneumonitis, as well as radiographic findings of ground glass or linear opacities that occurred within the first week of treatment with brigatinib (between 24 and 48 hours). Early in the clinical development of brigatinib, moderate to severe pulmonary adverse events were observed shortly after initiating treatment with the drug. In study AP26113-13-201, 6.4% of patients developed EOPE; 2.7% had Common Terminology Criteria for Adverse Events, Version 4(CTCAE) Grade 3-4 EOPE and 1 patient had fatal pneumonia that was characterized as EOPE. Of the patients experiencing CTCAE Grade 1-2 EOPE, brigatinib was interrupted and restarted, or the dose was reduced, and the patients remained on treatment. The EOPE occurred on the 90 mg QD dose regardless of the arm. In other words, for the patients in Arm B who developed EOPE, it occurred within the first week and no EOPE developed after the dose escalation to 180 mg QD in this arm. In study AP26113-11-101, there were two fatal EOPE events (hypoxia and pneumonia). In addition to EOPE, in study AP26113-13-201, 1.8% of patients experienced later onset pneumonitis, including one patient with CTCAE Grade 3 symptoms.

^h Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.1.1 Safe-Use Conditions

To mitigate the risks of pulmonary adverse events, including EOPE, the Prescribing Information (PI) will have a Warnings and Precautions statement; additionally, the PI will include recommendations for patient monitoring and dose reductions based on severity.

5.2 HYPERTENSION

Hypertension was identified as a treatment emergent adverse event (TEAE) in clinical studies of brigatinib. In the PI, hypertension is noted to have been reported in 21% of patients treated with brigatinib at the 180 mg dose, with 6.4% of those patients having CTCAE Grade 3 events.

5.2.1 Safe-Use Conditions

To mitigate the risk of hypertension, the Prescribing Information (PI) will have a Warnings and Precautions statement; additionally, the PI will include recommendations for patient monitoring and dose reductions based on severity.

6 Expected Postmarket Use

Brigatinib is an oral medication expected to be taken by patients at home as directed by their treating oncologists. These patients are expected to be followed in the outpatient setting by an oncologist experienced in the treatment of metastatic ALK + NSCLC and the risks associated with ALK inhibitors.

7 Discussion of Need for a REMS

Brigatinib is a kinase inhibitor indicated for the treatment of patients with ALK + metastatic NSCLC who have progressed on or are intolerant to crizotinib. Metastatic ALK positive (+) NSCLC is a serious medical condition with very poor survival rates. Patients with metastatic ALK + NSCLC who have developed resistance to crizotinib, and had disease progression are a narrow population who will likely die of their disease. Crizotinib was the first ALK-inhibitor approved for the treatment for ALK+ positive NSCLC. This drug was granted accelerated approval in 2011, followed by full approval in 2013. However, many patients have disease progression within 1-2 years, and up to one-third of patients develop ALK-dependent mechanisms of resistance.¹¹

Ceritinib (accelerated approval in 2014) and alectinib (accelerated approval in 2015) are 2 other ALK inhibitors with indications for the treatment of NSCLC in patients who have progressed on or are intolerant to crizotinib. Common risks among the currently approved ALK inhibitors include: pulmonary adverse events (pneumonitis and interstitial lung disease (ILD)), bradycardia, vision impairment, creatinine phosphokinase (CPK) elevation, pancreatic enzyme elevation, and embryo fetal toxicity seen in animal studies. None of these agents were approved with Boxed Warnings for any of these adverse events; all were communicated in the Warnings and Precautions section of their respective labels.^{12,13,14} Additionally, none of these products required a REMS to ensure the benefits outweighed the risks.

The risks associated with brigatinib are similar to the other approved TKIs for ALK+ NSCLC, and like the other drugs in this class will be described in labeling. The PI for brigatinib will include Warnings and Precautions describing the risks of pulmonary adverse reactions, hypertension, bradycardia, visual disturbance, creatine phosphokinase (CPK) elevation, pancreatic enzyme elevations, and embryo-fetal toxicity. The PI for brigatinib will also include monitoring recommendations and dose reductions/discontinuations based upon the severity of the toxicity, as well as a Patient Information sheet. If approved, similar to crizotinib, ceritinib, and, alectinib, the PI will not include a boxed warning.

Metastatic ALK + NSCLC is a serious medical condition with very poor survival and healthcare providers, typically medical oncologists, who treat metastatic ALK + NSCLC, should be familiar with the risks associated with ALK inhibitors, including the importance of patient monitoring.

8 CONCLUSION & RECOMMENDATIONS

DRISK and the Division of Oncology Products (DOP) II agree that a REMS is not necessary to ensure the benefits of brigatinib outweigh its risks.

If new safety information becomes available, please consult DRISK.

9 Materials Reviewed

The following is a list of materials informing this review:

1. Ariad. Proposed Prescribing Information for Alunbrig (brigatinib), August 29, 2016.
2. Ariad. Clinical Overview for brigatinib, August 29, 2016.
3. Ariad. Summary of Clinical Safety for brigatinib, August 29, 2016.
4. Ariad. Summary of Clinical Efficacy for brigatinib, August 29, 2016
5. Ariad. EU Risk Management Plan for brigatinib, August 23, 2016.
6. Donoghue, Martha. DOP 2. Review Designation Memo for brigatinib, NDA 208772. Submitted to DARRTS on September 20, 2016.
7. Interdisciplinary Review Team for QT Studies. Thorough QT Study Review, IND 110935. Submitted to DARRTs on September 8, 2015.
8. Horiba, Naomi; Ly, Thomas. DOP 2 and DB-V. Mid-Cycle Clinical & Statistics slides, NDA 208772, November 29, 2016.
9. Ariad. Draft package insert (PI), November 21, 2016.

10 REFERENCES

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 2. Cancer Facts & Figures 2016.
<http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf>, American Cancer Society, accessed 9/6/16.
 3. Shaw, AT, Solomon, B. Anaplastic lymphoma kinase (ALK) fusion oncogene positive non-small cell lung cancer. Up To Date. <http://www.uptodate.com/contents/anaplastic-lymphoma-kinase-alk-fusion-oncogene-positive-non-small-cell-lung-cancer>, accessed 9/6/16.
 4. Ariad. Risk Management Plan for Alunbrig (brigatinib), Version 1, August 23, 2016.
 5. Donoghue, Martha. Review Designation Memo dated September 20, 2016.
 6. Horiba, Naomi; Ly, Thomas. DOP 2 and DB-V. Mid-Cycle Clinical & Statistics slides, NDA 208772, November 29, 2016.
 7. Horiba, Naomi; Ly, Thomas. DOP 2 and DB-V. Mid-Cycle Clinical & Statistics slides, NDA 208772, November 29, 2016.
 8. Ariad. Risk Management Plan for Alunbrig (brigatinib), Version 1, August 23, 2016; 7-11.
 9. Axitinib (Inlyta®) USPI, Revised August 2014
 10. Cabozantinib (Cabometyx™) USPI, April 2016
 11. Katayama R et al. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. Clin Cancer Res. 2015;21:2221-35
 12. Crizotinib (Xalkori®) USPI, Revised April 2016
 13. Ceritinib (Zykadia®) USPI, Revised September 2016
 14. Alecetinib (Alecensa®) USPI, Revised November 2016

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