CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210498Orig1s000

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	210496 encorafenib; 210498 binimetinib
PDUFA Goal Date	June 29, 2018
OSE RCM #	2017-1307; 2017-1309
Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 28, 2017
Subject	Evaluation of the Need for a REMS
Established Name	encorafenib, binimetinib
Trade Name	Braftovi, Mektovi
Name of Applicant	Array Pharmaceuticals
Therapeutic class	Kinase Inhibitors
Formulation	50mg, and 75mg capsule (encorafenib); 15mg tablet (binimetinib)
Dosing Regimen	Encorafenib 450mg once daily orally with binimetinib 45mg twice daily orally.

Table of Contents

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 (NME) Braftovi (encorafenib) and Mektovi (binimetinib) is necessary to ensure the benefits outweigh its risks. Array BioPharma submitted a New Drug Application (NDA) 210496 for encorafenib with the proposed indication to be used in combination with binimetinib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. In addition, Array BioPharma also submitted a NDA 210498 for binimetinib for the same above indication, to be used in combination with encorafenib. This application is under review in the Division of Oncology Products 2 (DOP2).

The risks associated with encorafenib and binimetinib include new malignancies, cardiomyopathy, venous thromboembolism, ocular toxicities, and for encorafenib, mild elevations in the QT interval were seen in the clinical trials. These adverse events for encorafenib and binimetinib are similar to labeled events for other treatment combinations used for metastatic melanoma, and none of these events been proposed to be communicated in a Boxed Warning. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK believes that a REMS is not needed to ensure the benefits of encorafenib and binimetinib outweigh its risks. Encorafenib and binimetinib do not present with any significant clinical or different adverse events than other currently approved BRAF/MEK therapies for the treatment of metastatic melanoma, and provide another treatment option for this patient population.

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) Braftovi (encorafenib) and Mektovi (binimetinib) is necessary to ensure the benefits outweigh its risks. Array BioPharma submitted a New Drug Application (NDA) 210496 for encorafenib with the proposed indication to be used in combination with binimetinib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. In addition, Array BioPharma also submitted a NDA 210498 for binimetinib for the same above indication, to be used in combination with encorafenib. This application is under review in the Division of Oncology Products 2 (DOP2). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Encorafenib and binimetinib are both kinase inhibitors, though they both target two different kinases in the RAS/RAF/MEK/ERK pathway. Encorafenib targets BRAF V600E, as well as wild-type BRAF and CRAF in addition to other kinases such as JNK1, JNK2, JNK3, LIMK1, LIMK2, MEK4, PFCDPK1 and STK36 to reduce ligand binding and inhibit growth of tumor cell lines.[1] Binimetinib is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activity. These proteins are upstream regulators of extracellular signal-related kinases (ERK) which prevents phosphorylation and tumor

growth in BRAF-mutant murine models.[2] The recommended dose of encorafenib is 450 mg orally once daily in combination with binimetinib and the recommended dose of binimetinib is 45 mg orally twice daily in combination with encorafenib until disease progression or unacceptable toxicity. Encorafenib is available as 50 mg and 75 mg capsules, and binimetinib is available as 15 mg tablets.[a]

The intended setting in which the drug is likely to be administered is in an outpatient setting while the patient is under the care of the treating oncologist. These drugs are not part of a class of kinase inhibitors that have a REMS or a Boxed Warning, and both drugs are considered NMEs.[b]

Neither drug was granted orphan drug or breakthrough therapy. Both applications are under Priority Review. Encorafenib and binimetinib are not marketed in any other jurisdictions.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDAs 210496 encorafenib and 210498 binimetinib relevant to this review:

- 02/06/2017: Applicant informed at pre-NDA meeting that a REMS for encorafenib and binimetinib was not needed for submission, but a final review would be made upon determination of the applications.
- 06/30/2017: NDA 210496 encorafenib and NDA 210498 binimetinib submissions received
- 12/04/2017: 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 encorafenib and binimetinib
- 06/29/2018: Prescription Drug User Fee Act (PDUFA) date

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Metastatic melanoma accounts for approximately one percent of skin cancers but causes the majority of deaths due to its ability to metastasize to several vital organs quickly, such as the brain, lungs and liver.[c,3,4] The rates of melanoma have been steadily rising over the last 30 years. In the United States, 91,270 new melanomas will be diagnosed, and of that, 9,320 people are expected to die from melanoma.[4,d] Approximately 50% of patients with metastatic melanoma have mutations in BRAF and

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

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

[c] 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.*

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

about 95% of these are in BRAF V60015.[5] Prognostic factors are the site of metastases, age of onset, degree of skin damage, and stage of disease. In Stage IV, the 5-year survival rate is 15-20%.[4]

3.2 Description of Current Treatment Options

National Comprehensive Cancer Network (NCCN) Guidelines recommend that first line treatment of BRAF-mutated metastatic melanoma include checkpoint inhibitor therapies, or combination therapy with BRAF and MEK inhibitors.[6]

The following is a summary of FDA approved treatments for BRAF-positive metastatic melanoma.[7]

Targeted Monotherapy:

- Vemurafenib (BRAF inhibitor) approved 2011
- Dabrafenib (BRAF inhibitor) approved 2013
- Trametinib (MEK inhibitor) approved 2013

Targeted Agents in Combination:

- Trametinib and dabrafenib approved 2014
- Vemurafenib with Cobimetinib (NME Kinase inhibitor, approved 2015) both approved 2015

Checkpoint Inhibitors Monotherapy:

- Ipilimumab (anti CTLA-4 antibody) approved 2011
- Nivolumab (anti PD-1 antibody) approved 2014
- Pembrolizumab (anti-PD-1 antibody) approved 2014

Checkpoint Inhibitors in Combination

- Nivolumab and Ipilimumab approved 2015

Of these therapies, vemurafenib, dabrafenib, trametinib and cobimetinib are most like encorafenib and binimetinib based on mechanism of action and target of therapy. None of these drugs were approved with Boxed Warnings or a REMS.[8,9,10,11]

4 Benefit Assessment

Encorafenib and Binimetinib: [1,2,7]

Encorafenib in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to have received prior adjuvant therapy, not including a BRAF or MEK inhibitor, and up to one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Patients were randomized (1:1:1) to receive encorafenib 450 mg once daily in combination with binimetinib 45 mg twice daily (encorafenib in combination with binimetinib), BRAFTOVI 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity. The major efficacy outcome measure was progression-free survival

(PFS) of BRAFTOVI in combination with binimetinib compared with vemurafenib as assessed by a blinded independent review. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurred first. Other outcome measures included objective response rate (ORR) and duration of response (DoR) are highlighted below:

Table 1: Efficacy Results for COLUMBUS

	Encorafenib with binimetinib N = 192	**Vemurafenib N = 191**
Progression Free Survival		
Number of events (%)	98 (51)	106 (55)
Progressive disease	88 (46)	104 (54)
Death	10 (5)	2 (1)
Median PFS in months (95% CI)	14.9 (11, 18.5)	7.3 (5.6, 8.2)
Hazard Ratio (95% CI)	0.54 (0.41, 0.71)	
P value	<0.0001	
Overall Response Rate		
ORR (95% CI)	63% (56%, 70%)	40% (33%, 48%)
Complete Response	8%	6%
Partial Response	55%	35%
Duration of Response		
Median DoR in months (95%CI)	14.7 (9.4, 17.3)	6.4 (3.9 11)

As per the clinical reviewer at the midcycle review meeting, there is an overall positive benefit-risk profile for the combination regimen of encorafenib 450 mg orally once daily given with binimetinib 45 mg orally twice daily for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.[e]

5 Risk Assessment & Safe-Use Conditions

As per the clinical review team, the safety profile of encorafenib 450 mg plus binimetinib 45 mg is consistent with other BRAF-MEK inhibitor combinations as described in section 3.2 of this review. Primary risks under evaluation include: new malignancies, cardiac toxicities, venous thromboembolism,

[e] 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.*

and ocular toxicities. For encorafenib, QTc prolongation was noted as an adverse event. Risk management of these events include discussion of these events in Warnings and Precautions of labeling as well as a Medication Guide as seen with the other BRAF-MEK inhibitors. There are currently no Boxed Warnings for encorafenib or binimetinib.[1,2,f]

5.1 NEW PRIMARY MALIGNANCIES

Based on its mechanism of action, encorafenib may promote growth and development of malignancies with activation of RAS through mutation or other mechanisms. In COLUMBUS, cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma (KA), occurred in 2.6% and basal cell carcinoma in 1.6% of patients who received binimetinib in combination with encorafenib. Median time to first occurrence of cuSCC/KA was 5.8 months (range 1 - 9 months).[1,2]

5.2 CARDIOMYOPATHY

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, can occur when binimetinib is administered in combination with encorafenib. Grade 3 left ventricular dysfunction occurred in 1.6%. In COLUMBUS, the median time to first occurrence of LVEF dysfunction (any grade) in patients receiving encorafenib in combination with binimetinib was 3.6 months (range 0 to 21 months). Cardiomyopathy resolved in 87% of patients receiving binimetinib plus encorafenib.[1]

Labeling will recommend that prescribers assess LVEF by echocardiogram or MUGA scan prior to initiating treatment, one month after initiation, and then every 2 to 3 months during treatment. The safety of binimetinib in combination with encorafenib has not been established in patients with a baseline LVEF that is either below 50% or below the institutional lower limit of normal (LLN).[1,2]

5.3 VENOUS THROMBOEMBOLISM

In COLUMBUS, venous thromboembolism (VTE) occurred in 5.7% of patients receiving binimetinib plus encorafenib, including 3.1% of patients who developed pulmonary embolism. Labeling will recommend that prescribers withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.[1,2]

5.4 QTC PROLONGATION – ENCORAFENIB

Encorafenib is associated with dose-dependent QTc interval prolongation. In COLUMBUS, an increase from baseline > 30 ms was measured in 27% of patients and > 60 ms was measured in 5.4% who received encorafenib in combination with binimetinib. The mean QTcF change from baseline was 18 (14 to 22) ms. A QTcF > 500 ms was measured in 0.5% of patients who received encorafenib in combination with binimetinib. In patients who received encorafenib alone, 2.8% were found to have a QTcF > 500 ms.

(b) (4) 1

[f] 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.*

Labeling will recommend that [redacted] (b) (4) Avoid the use of encorafenib in patients who already have or who are at significant risk of developing QTc prolongation, including patients with congenital long QT syndrome, uncontrolled or significant cardiac disease or conduction abnormalities such as congestive heart failure, bradyarrhythmias, and electrolyte abnormalities. Avoid the use of encorafenib with drugs known to prolong the QTc interval.[1]

5.5 OCULAR TOXICITIES

Serous retinopathy and Retinal Vein Occlusion (RVO)[1,2]

In COLUMBUS, serous retinopathy occurred in 20% of patients treated with MEKTOVI plus encorafenib; 7.8% were retinal detachment and 5.7% were macular edema. Symptomatic serous retinopathy occurred in 7.8% of patients with no cases of blindness. No patient discontinued binimetinib due to serous retinopathy. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months (0 to 17.5 months).

Retinal vein occlusion is a known class-related adverse reaction MEK inhibitors and may occur in patients treated with binimetinib and encorafenib. In patients receiving this combination, 1 patient experienced RVO.

The label will recommend that prescribers assess for visual symptoms at each visit. Perform an ophthalmological evaluation at regular intervals and anytime a patient reports new or worsening visual disturbances.

6 Expected Postmarket Use

Encorafenib in combination with binimetinib is expected to be prescribed by oncologists to patients with metastatic melanoma on an outpatient basis.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for encorafenib or binimetinib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of encorafenib and binimetinib based on the efficacy and safety information currently available.

Encorafenib and binimetinib are kinase inhibitors being proposed to be used in combination with each other for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. Adverse events noted with this drug combination include the same adverse events as described with other BRAF/MEK inhibitors trametinib, dabrafenib, vemurafenib, and cobimetinib which are: new primary malignancies, cardiomyopathies, venous thromboembolism, and ocular events, all of which are communicated in the Warnings and Precautions

of these drugs. Encorafenib and binimetinib will also have these adverse events communicated in Warnings and Precautions.

QT interval prolongation is an adverse event noted with encorafenib. As per the clinical QT-IRT consult, even though encorafenib shows a dose and concentration dependent QTc interval prolongation, there is a lack of direct relationship between concentrations of encorafenib and QTc effects because of temporal increases.[12] Recommendations were to describe this relationship, as well as the clinical information presented in the Applicant's clinical trial in Warnings and Precautions, as the change in the QT interval were not to a large degree. The mean QTcF change from encorafenib from baseline was 18 (14 to 22) ms. Increases in QTcF are adverse events associated with for this drug class, and are communicated in Warnings and Precautions for other kinase inhibitors. Vandetinib, a kinase inhibitor for the treatment of medullary thyroid cancer, is the only kinase inhibitor with a Boxed Warning and a REMS with elements to assure safe use (ETASU) for the risk of increases in QTcF. The mean change in the QTcF interval for vandetinib was 35ms, with 36% of patients having a QTcF change more than 60ms, and 4.3% of patients experiencing changes >500ms.[13]

The adverse events reported for encorafenib and binimetinib are similar to labeled events for currently approved BRAF/MEK therapies for the treatment of metastatic melanoma and provide another treatment option for this patient population. Therefore, this DRISK reviewer does not recommend a REMS for either encorafenib or binimetinib.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore a REMS is not necessary for encorafenib and binimetinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated.

10 REFERENCES

[1] Braftovi draft labeling February 21, 2018

[2] Mektovi draft labeling February 21, 2018

[3] Ali Z et al. Melanoma epidemiology, biology and prognosis. EJC Suppl. 2013;11(2):81-91

[4] https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html accessed 2/18/2018

[5] Colombino M et al. BRAF/NRAS mutation frequiences among primary tumors and metastases in patients with melanoma. J Clin Oncol 2012; 30(20): 2522-9.

[6] NCCN Cancer Guidelines Metastatic Melanoma, March 2017

[7] Braftovi and Mektovi Clinical Midcycle Meeting slides, November 30, 2017

[8] Zelboraf (vemurafenib) Prescribing Information, Genentech Inc., updated November 2017

[9] Tafinlar (dabrafenib) Prescribing Information, Novartis Pharmaceuticals Corporation, updated June 2017

[10] Mekinist (trametinib) Prescribing Information, Novartis Pharmaceutical Corporation, updated June 2017

[11] Cotellic (cobimetinib) Prescribing Information, Genentech Inc., updated January 2018

[12] Interdisciplinary Review Team for QT Studies Consultation: QT Study Review for Encorafenib. DARRTS, December 4, 2017

[13] Caprelsa (vandetinib) Prescribing Information, Genzyme Corporation, updated December 2016

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/s/

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02/28/2018

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