

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206192Orig1s000

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

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: May 22, 2015

Reviewer(s): Amariyls Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Naomi Redd, Pharm.D., Acting Team leader, DRISK
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Drug Name(s): Cobimetinib (Cotellic[®])

Therapeutic Class: Mitogen-activated protein kinases 1 and 2 (MEK1 and MEK2) inhibitor

Dosage and Route: Cobimetinib 60 mg PO QD Days 1-21 of each 28-day treatment cycle in combination with vemurafenib 960 mg PO BID on Days 1-28

Application Type/Number: NDA 206192

Submission Number: Seq. No. 0000 (1) and 0009 (10)

Applicant/sponsor: Genentech

OSE RCM #: 2014-2486 and 2014-2483

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1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of whether a risk evaluation and mitigation strategy (REMS) is necessary for cobimetinib (NDA 206192, received by FDA on October 30, 2014). Genentech is seeking approval for cobimetinib (Cotellic[®]) to be used in combination with vemurafenib (Zelboraf[®], NDA 202429) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.

Genentech did not submit a REMS with this application but, at the request of FDA, submitted the Company Core Risk Management Plan (cRMP) on February 6, 2015.

2 REGULATORY HISTORY

The regulatory history of cobimetinib, pertinent to this review, is as follows:

- **November 21, 2013:** Orphan-drug designation granted for the treatment of stage IIb, IIc, III and IV melanoma with kBRAF V600E mutation.
- **October 8, 2014:** Pre-NDA – type B. FDA indicated that a REMS was not required.
- **October 30, 2014:** FDA Receives NDA 206192 for cobimetinib.
- **February 4, 2015:** FDA Request for information on available pharmacovigilance plan.
- **February 6, 2015:** Sponsor submitted pharmacovigilance plans and the Company Core Risk Management Plan (cRMP).
- **February 13, 2015:** Priority review designation granted and proposed proprietary name, Cotellic, conditionally approved.
- **March 6, 2015:** Mid-cycle review meeting.

Important upcoming dates include the following:

- **August 11, 2015:** PDUFA date.

3 MATERIALS REVIEWED

3.1 DATA AND INFORMATION SOURCES

- Cobimetinib NDA Introduction and Clinical Overview received by FDA on December 11, 2014.
- Genentech response to FDA's information request for a pharmacovigilance plan received by FDA on February 6, 2015 (included a Risk Management Plan).
- Cobimetinib mid-cycle review meeting slides, dated March 6, 2015.
- Draft Clinical Review, Ruthann Giusti, DOP2, dated May 12, 2015.

4 ASSESSMENT OF NEED FOR A REMS

4.1 RATIONALE FOR DRUG DEVELOPMENT^{1,2}

Malignant melanoma is the 5th most prevalent cancer in men and the 6th most common in women in the United States. The median age at diagnosis for melanoma is 59 years, and approximately 21% of the patients are under 45 years of age at the time of diagnosis. Around 2 and 5% of patients will present with metastatic disease. Metastatic or unresectable melanoma is associated with high rates of morbidity and mortality. Survival time for patients with metastatic disease ranges from 6 to 9 months with long-term survival of less than 10%.

The mitogen-activated protein kinase 1 and 2 (MEK1 and MEK2) are key components of the RAS/RAF/MEK/ERK signal transduction pathway, a highly conserved signaling pathway which plays an important role in cell proliferation, survival, migration, cell-cycle regulation, and angiogenesis. In the absence of typical growth factors, mutations in BRAF gene result in activation of the RAF-MEK-ERK pathway which may result in excessive cell proliferation and survival. The BRAF mutation is found in approximately 50% of malignant melanoma tumors. Monotherapy with BRAF inhibitors has significantly improved the clinical course of BRAF-mutated melanoma patients but the benefit can be short-lived due to the development of resistance to therapy driven by upregulated MAPK/MEK signaling. The addition of a MEK inhibitor to a BRAF inhibitor can overcome acquired resistance to BRAF inhibition and can delay the onset of acquired resistance to BRAF inhibitors.

There are few treatment options for patients with unresectable melanoma including single-agent chemotherapy, combination chemotherapy, biotherapy, biochemotherapy, radiation therapy, and vaccines. FDA-approved treatment alternatives include: dacarbazine (multiple NDAs and ANDAs), ipilimumab (Yervoy[®], BLA 125377), vemurafenib, dabrafenib (Tafinlar[®], NDA 202806), trametinib (Mekinist[™], NDA 204114), and pembrolizumab (Keytruda[®], BLA 125514).

Vemurafenib and dabrafenib are FDA approved BRAF inhibitors indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Trametinib is a reversible inhibitor of MEK1 and MEK2 activation and of MEK1 and MEK2 kinase activity.³ Trametinib monotherapy and in combination with dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. Trametinib's label includes Warning and Precautions for the following:

- New primary malignancies

¹ Cobimetinib Clinical Overview, page 9-10.

² Kim K.B., Davies M.A., Rapini R.P., Hwu P, Bedikian A.Y. (2011). Chapter 39. Malignant Melanoma. In Kantarjian H.M., Wolff R.A., Koller C.A. (Eds), *The MD Anderson Manual of Medical Oncology*, 2e. Retrieved April 10, 2015 from <http://accessmedicine.mhmedical.com/content.aspx?bookid=379&Sectionid=39902069>.

³ Mekinist product label, accessed on April 7, 2015 at <http://dailymed.nlm.nih.gov>.

- Hemorrhage
- Venous thromboembolism
- Cardiomyopathy
- Ocular toxicities (retinal vein occlusion, retinal pigment epithelial detachment, uveitis and iritis)
- Interstitial lung disease
- Serious febrile reactions
- Serious skin toxicity
- Hyperglycemia
- Embryofetal toxicity

There is a medical need for additional safe and effective therapeutic options for this disease, particularly for those which will also decrease the emergence of resistance to BRAF inhibitors. Cobimetinib is a synthetically manufactured small molecule inhibitor of MEK1 and MEK2 developed to be used in combination with vemurafenib. Cobimetinib is formulated as a film-coated 20 mg oral tablet. The recommended dose is 60 mg orally once daily for the first 21 days of each 28 days in combination with vemurafenib.

4.2 CLINICAL DEVELOPMENT PROGRAM⁴

Data to support this application are derived primarily from the pivotal phase III study GO28141 and supporting efficacy, safety and pharmacokinetics data obtained from the Phase Ib study NO25395 (BRIM7). Additional safety and pharmacokinetics data are derived from the phase I single agent study MEK4592g in patients with advanced solid tumors, and from clinical pharmacology studies. Safety analyses were based on safety information from the 3 studies (i.e., GO28141, NO25395 and MEK4592g). The integrated safety population included data pooled from all patients treated with cobimetinib plus vemurafenib in Study GO28141 (n=254) and Study NO25395 (n=129).

4.2.1 Efficacy

Study GO28141 is double-blind, randomized trial, in which 495 patients with advanced BRAF V600-mutated melanoma who had received no previous treatment for advanced disease were randomized to receive cobimetinib plus vemurafenib or placebo plus vemurafenib. Study GO28141 demonstrated a statistically significant reduction in the hazard rate of disease progression or death with the combination of cobimetinib and vemurafenib (HR 0.50 (95% CI: 0.38, 0.67; p<0.0001)). The median progression free survival (PFS) was estimated to be 9.9 months (95% CI: 9.0, NR) for the cobimetinib/vemurafenib treatment group and 6.2 months (95% CI: 5.6, 7.4) for the placebo/vemurafenib treatment group. Secondary endpoints (e.g., overall survival, objective response rate (ORR), duration of response) also support the efficacy of cobimetinib in combination with vemurafenib.

Study NO25395 is an open-label, dose-escalation and expansion phase Ib study of

⁴ Cobimetinib NDA Introduction and Clinical Overview, received by FDA on December 11, 2014.

cobimetinib in combination with vemurafenib in patients with advanced BRAF V600-mutated melanoma. This study included patients who had not been treated with a BRAF inhibitor and patients who had recently progressed on vemurafenib also provided supportive evidence of efficacy.

4.2.2 Safety⁵

The most common adverse events were diarrhea, photosensitivity, nausea, creatine phosphokinase (CPK) increase, pyrexia and vomiting. Safety concerns identified by the sponsor and included in their proposed risk management plan include serous retinopathy (24% of patients treated with the cobimetinib plus vemurafenib; chorioretinopathy or retinal detachment), teratogenicity (embryo-lethality and fetal malformations of the great vessels and skull at clinically relevant exposures in rats), and left ventricular dysfunction (grade ≥ 2 decrease in LVEF from baseline reported in 6.7% of patients on cobimetinib plus vemurafenib). Additional serious safety concerns associated with the use of cobimetinib in combination with vemurafenib include cutaneous malignancies, photosensitivity, and liver laboratory abnormalities. Basal cell carcinoma was reported in 4% of patients receiving cobimetinib plus vemurafenib compared to 2% of patients receiving vemurafenib alone. Photosensitivity was reported in 41% of patients receiving cobimetinib plus vemurafenib. Liver laboratory abnormalities, specifically increases in alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, have been observed in patients treated with cobimetinib plus vemurafenib (all grades: 66%, 69%, and 69% respectively).

4.2.3 Overall Benefit:Risk Assessment

The Division of Oncology Products 2 (DOP2) determined that the risk-benefit assessment is favorable for the use of cobimetinib in combination with vemurafenib in the treatment of patients with BRAF V600E or V600 K mutation-positive unresectable or metastatic melanoma.

4.3 RISK MANAGEMENT APPROACH

The proposed risk management plan submitted by the sponsor does not include risk management measures beyond labeling to manage the serious risks associated with cobimetinib.

If approved, the benefit:risk profile of cobimetinib is favorable for use in combination with vemurafenib in the treatment of patients with BRAF V600E or V600 K mutation-positive unresectable or metastatic melanoma without a REMS. The safety profile of cobimetinib (i.e., left ventricular dysfunction, new primary cutaneous malignancies, serious retinopathy, photosensitivity, liver functions abnormalities, and embryo-fetal toxicity) is similar to that of trametinib, the other drug in the class. The serious risks associated to trametinib are communicated through labeling. Regarding the risk of teratogenicity, the anticipated patient population for cobimetinib is narrow and includes patients with a life-threatening disease. The anticipated prescriber population would be

⁵ Cotellic draft product label, received by FDA on April 6, 2015.

likely limited to oncologists with experience in the management of the risk of teratogenicity.

Past regulatory actions for mitigating the risk of teratogenicity for oncology drugs such as vismodegib, crizotinib, vemurafenib, trametinib consisted of communicating this risk through labeling only. Similar to cobimetinib, these products are primarily prescribed by oncologists to relatively narrow populations of patients with life-threatening diseases for which there are limited treatment options. Therefore, DRISK recommends communicating the risk of teratogenicity and the other serious risks identified with the use of cobimetinib (listed above) through labeling only.

In addition to labeling (i.e., patient counseling information and FDA-approved patient labeling information) FDA is requesting the sponsor conduct postmarketing studies to assess the incidence, severity, and reversibility of ocular toxicities and to monitor for cutaneous and non-cutaneous malignancies.

5 CONCLUSION AND RECOMMENDATIONS

The clinical development program for cobimetinib demonstrated that, in combination with vemurafenib, this drug is effective in the management of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation. At this time, DRISK and the Division of Oncology Products 2 determined that a REMS is not necessary to ensure the benefits outweigh the serious risks associated with cobimetinib and these risks will be communicated through product labeling as with the other drug in the class which shares a similar risk profile.

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/s/

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05/26/2015

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