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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur
Subject	Office Director Summary Review
NDA	NDA 206192
Applicant Name	Genentech
Date of Submission	December 11, 2014
Major Amendment Received	June 15, 2015
PDUFA Goal Date	November 11, 2015
Proprietary Name / Established (USAN) Name	Cotellic/ cobimetinib
Dosage Forms / Strength	Tablets for oral administration/ 20-mg
Proposed Indication(s)	For use in combination with Zelboraf (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director Review	Patricia Keegan
CDTL Review	Marc Theoret
Regulatory Project Manager Review	Meredith Libeg
Medical Officer Review	Ruthann Giusti
Statistical Review	Xiaoping (Janet) Jiang
Pharmacology Toxicology Review	Shawna L. Weis & M. Anwar Goheer
Quality Review	Olen Stephens (Technical Lead), Gaetan Ladouceur (Drug Substance), Donghao Lu (Drug Product), Zengfang Ge (Process, Microbiology), Sunita Iyer (Facility), Maziar Kakhi (Biopharmaceutics)
Clinical Pharmacology Review	Ruby Leong
OSI	Lauren Iacono-Connors
OSE/DMEPA	Otto Townsend
OSE/DRISK	Amarilys Vega
Ophthalmology Review	Wiley Chambers
QT IRT Consult Review	Dinko Rekic
Controlled Substances Staff Review	Katherine Bonson
DPMH Review	Miriam Dinatale

OND=Office of New Drugs
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
QT IRT=QT Interdisciplinary Review Team
DPHM=Division of Pediatric and Maternal Health

1. Introduction & Background

On December 11, 2014, Genentech submitted an NDA for cobimetinib (Cotellic); a reversible, non-ATP-competitive inhibitor of the mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. These proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. In patients with melanoma containing BRAF V600E or BRAF V600K mutations, the ERK pathway is constitutively activated, resulting in promotion of tumor growth, which can be inhibited in nonclinical studies with exposure to cobimetinib.

Based on the Surveillance, Epidemiology, and End Results (SEER) Program, there will be an estimated 73,870 new cases and 9,940 deaths due to melanoma in the United States in 2015.[1] Of these new cases, 4% will be metastatic at diagnosis with a projected 5-year survival rate of 17%. Approximately half of the patients with metastatic melanoma will have detectable mutations in the *BRAF V600* gene in tumor specimens. Based on review of published literature, the presence of *BRAF V600* mutations may be a poor prognostic factor for survival[2].

Vemurafenib was approved on August 17, 2011, for the treatment of patients with unresectable or metastatic melanoma with BRAF-V600E mutation as detected by an FDA-approved test. Vemurafenib is not recommended for use in patients with wild-type BRAF melanoma. This approval was based on demonstration of a clinically important and statistically significant improvement in overall survival (OS) as compared to dacarbazine; based on updated results, the median OS was 13.6 months vs 10.3 months for vemurafenib and dacarbazine, respectively. This was supported by demonstration of improvements in progression-free survival (PFS) (5.3 vs. 1.6 months) and overall response rates (ORR) (48.4% vs. 5.5%).

Ipilimumab was approved on March 25, 2011, for the treatment of unresectable or metastatic melanoma. This approval was based on demonstration of a clinically important and statistically significant improvement in OS as compared to an investigational vaccine, with median survivals of 10 months for ipilimumab vs. 6 months for the investigational vaccine. These results were supported by demonstration of improved survival in a second trial comparing ipilimumab with dacarbazine.

Dabrafenib was approved on May 29, 2013, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations, as detected by an FDA-approved test. Dabrafenib is not indicated for the treatment of patients who have received prior BRAF-inhibitor therapy. This approval was based on demonstration of a clinically important improvement in PFS as compared to dacarbazine, with a median PFS of 5.1 months and 2.7 months for dabrafenib and dacarbazine, respectively, and supported by improvement in ORR (52% vs. 17%).

Trametinib was approved on May 29, 2013, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or BRAF V600K mutations, as detected by an FDA-approved test. Trametinib is not indicated for the treatment of patients who have received prior BRAF-inhibitor therapy. This approval was based on demonstration of a clinically important improvement in PFS as compared to chemotherapy (dacarbazine or paclitaxel) with a median PFS of 4.8 months in the trametinib arm as compared to 1.5 months in the chemotherapy arm.

Other FDA-approved drugs: There are additional drugs which are approved for a broader population of patients with unresectable or metastatic melanoma (i.e., regardless of BRAF mutation status), which include pembrolizumab, nivolumab, aldesleukin, and dacarbazine. In addition, there are two drugs approved in combination for treatment of patients with BRAF mutation-positive melanoma. These other drugs are not considered "available therapy" for the following reasons:

- Dacarbazine is no longer relevant to the US standard of care for this patient population, since the approvals of vemurafenib, dabrafenib.
- Aldesleukin is indicated only for patients with excellent performance status and end-organ function; it is administered at high doses requiring intensive cardiopulmonary monitoring and support. Therefore its use is limited to the specialized medical centers and thus is not considered part of the US standard of care at most institutions.

[1] http://seer.cancer.gov/statfacts/html/melan.html. Accessed November 2, 2015.

[2] Impact of BRAF mutation status in the prognosis of cutaneous melanoma: an area of ongoing research. Bhatia P, Friedlander P, Zakaria EA, Ann Transl Med. Feb; 3(2): 24, 2015.

- Pembrolizumab, as a single agent, and nivolumab, as a single agent, were approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) based on demonstration of an effect on a surrogate endpoint (durable responses) and therefore are not considered available therapy.
- Dabrafenib and trametinib for use in combination were approved under the provisions of 21 CFR 314 Subpart H (accelerated approval) based on demonstration of an effect on a surrogate endpoint (durable responses) and therefore are not considered available therapy.

2. CMC/Biopharmaceutics

There are no issues that would preclude approval from a CMC perspective. Chemistry, microbiology, biopharmaceutics, and facility reviewers provided an overall acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 30 months when stored at room temperature below 30°C (86°F).

3. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from a nonclinical perspective. The NDA contained nonclinical data which supported the proposed mechanism of action of reversible, non-ATP-competitive inhibitor of MEK1 and MEK2 signaling. In addition, binding of cobimetinib to the μ-opioid receptor was demonstrated. In murine xenografts, cobimetinib administration, alone or with vemurafenib, delayed tumor growth in animals bearing in BRAF V600E melanoma xenografts.

The results of 4-week and 13-week general toxicology studies identified skin and the GI tract as the major organs of toxicity in rats and dogs, respectively. Additional organs affected were liver, kidney, thyroid, adrenals, thymus, and lymph nodes. No dedicated fertility studies were conducted, however nonclinical toxicology studies in rats demonstrated effects on reproductive organs in rats (ovarian necrosis, decreases in corpora lutea, cysts and increased vaginal epithelial cell apoptosis), suggesting potential impairment in fertility.

Also noted in rats was a statistically significant but possibly clinically unimportant, 18% reduction in respiratory rate in rats receiving cobimetinib at a dose of 300 mg/kg. This finding was noted because of the binding to the μ-opioid receptor nonclinically. Since the interpretation of these findings was unclear, the potential for opioid effects was evaluated in the clinical study and the nonclinical review team consulted the Controlled Substance Staff (CSS) regarding the potential for abuse liability with cobimetinib.

In the embryofetal toxicology study conducted in rats, maternal toxicity was observed at exposures below that expected at the recommended dose; embryofetal effects included an increased rate of early resorption, total litter loss, and markedly increased post-implantation loss. Decreased fetal body weights, an increase in skeletal alterations, including decreased ossification malformations of the great vessels (missing and/or misplaced great vessels), and malformations of the eye sockets were also observed. While the nonclinical toxicology review notes that an additional embryofetal study may be required, the data provided were subsequently determined to be sufficient to inform labeling.

Cobimetinib was shown to inhibit hERG channel activity with an intermediate affinity (with an IC50 of 0.5 μM when tested alone and 0.6 μM when tested in combination with vemurafenib). No cardiovascular effects were observed in dogs at peak exposures 2-fold higher than that predicted in clinical studies. The interpretation of these finding was that there was a low risk for QT prolongation, which should be further investigated in clinical studies.

Cobimetinib was not mutagenic in the Ames bacterial mutagenicity assay and was negative for induction of structural abnormalities in the in vitro and chromosome aberration assay and in the in vivo micronucleus assay. (b) (4)

4. Clinical Pharmacology/Pharmacometrics

There are no issues that would preclude approval from a clinical pharmacology perspective. The NDA contained the results of pharmacokinetics (PK) studies evaluating the PK of cobimetinib alone and when administered with vemurafenib in patients with cancer (primarily metastatic melanoma), food effects studies, studies characterizing absorption, distribution, metabolism, excretion (ADME), drug interactions based on CYP enzymes and transporters. Since the formulation of cobimetinib was modified during the clinical development program, absolute bioavailability and relative bioavailability studies were conducted to support the use of data obtained with the previous formulation (capsule) used in clinical trials in support of the to-be-marketed formulation (tablet). The NDA also contained population PK analyses, exposure-response analyses for efficacy and safety, and assessment of effects on QTc based on serial ECGs obtained in clinical trials.

Cobimetinib administered at 60 mg daily has a half-life of 44 hours; based on this long half-life, product labeling states that missed doses should not be made up. Food effects studies indicate that there is no clinically important difference in exposure when cobimetinib is taken with a high-fat meal or fasting. The major route of metabolism is via the liver, with CYP3A oxidation and UGT2B7 glucuronidation; as discussed below, strong CYP3A inhibitors and inducers have substantial, clinically important effects on exposure. Coadministration of cobimetinib with a strong CYP3A inhibitor resulted in a 6.7-fold increase in cobimetinib exposure. Based on the magnitude of the effect on exposure, product labeling states that the dose of cobimetinib should be decreased from 60 mg to 20 mg daily and patients taking a reduced dose of cobimetinib (40 mg or 20 mg) should not take concomitant strong CYP3A inhibitors as there is no predicted safe dose of cobimetinib. In addition, product labeling notes that administration of a strong CYP3A inducer reduced cobimetinib exposure by more than 80%, which is likely to reduce efficacy.

The population PK analyses indicated that age, sex, and race/ethnicity did not have clinically important effects on cobimetinib exposure. The NDA did not contain the results of a dedicated hepatic impairment study or a dedicated renal impairment study. While population PK analyses supported the safety of dosing in patients with mild or moderate renal impairment at the recommended dose, there was insufficient data to assess the pharmacokinetics of cobimetinib in patients with severe renal impairment. Since the ADME study showed that renal excretion is not a major route of elimination and based on the popPK studies showing no clinically important effects of mild or moderate renal impairment on exposure, a dedicated renal impairment study has not been required. There is insufficient data based on population PK studies to make recommendations on dosing in patients with moderate or severe hepatic impairment. Since the liver is the major route of metabolism, a post-marketing requirement has been required to conduct a dedicated study in patients with mild and moderate hepatic impairment.

The dose chosen for clinical studies (cobimetinib 60 mg daily) was based on evidence of inhibition of the ERK signaling pathway in vitro and on dose finding studies to determine the maximum tolerated dose and clinical activity of cobimetinib and vemurafenib (Study NO25395). There were no evidence of an exposure-response (ER) relationship for efficacy (progression-free survival PFS) or for toxicity (Grade ≥ 3 rash, diarrhea; Grade ≥ 2 creatine phosphokinase elevation, photosensitivity, laboratory elevations in ALT, AST, alkaline phosphatase or total bilirubin; any grade retinal detachment or serous retinopathy).

Clinically important increases in QTc have been identified with administration of vemurafenib 960 mg twice daily. Based on ECGs obtained in the major efficacy trial, there was no evidence of additional effects on QTc with the addition of cobimetinib to vemurafenib as compared to vemurafenib alone.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

This NDA is supported by the results of a single, adequate and well-controlled, multicenter, international, randomized (1:1), open-label trial, Study GO28141. Key eligibility criteria were previously untreated, BRAF V600 mutation-positive unresectable or metastatic melanoma. The presence of BRAF V600 mutation was detected using the cobas® 4800 BRAF V600 mutation test. All patients received vemurafenib 960 mg orally twice daily on days 1-28 and were randomized (1:1) to receive cobimetinib 60 mg or

matching placebo orally once daily on days 1-21 of an every 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographic region (North America vs. Europe vs. Australia/New Zealand/others) and disease stage (unresectable Stage IIIc, M1a, or M1b vs. Stage M1c). Patients randomized to receive placebo were not allowed to receive cobimetinib at the time of progression. The primary endpoint of this trial was investigator-assessed PFS; key secondary endpoints were investigator-assessed confirmed ORR, OS, and PFS as assessed by blinded independent central review. Patients with available tumor samples were retrospectively tested using next generation sequencing to identify the BRAF mutation subtype (BRAF V600E or V600K). BRAF mutation subtype could be determined in 81% of the study population; 86% of these patients had BRAF V600E mutation-positive melanoma and 14% had BRAF V600K mutation-positive melanoma.

The trial showed a statistically significant improvement in PFS [HR: 0.56 (95% CI: 0.45, 0.70), $p < 0.001$] for patients randomized to receive cobimetinib with vemurafenib compared to those randomized to receive placebo with vemurafenib. The estimated median PFS was 12.3 months (95% CI: 9.5, 13.4) for patients randomized to receive cobimetinib with vemurafenib and 7.2 months (95% CI: 5.6, 7.5) for the patients randomized to receive placebo with vemurafenib. In addition, the trial also showed a statistically significant improvement in OS [HR: 0.63 (95% CI: 0.47, 0.85); stratified log-rank p-value=0.0019 (nominal significance level of 0.019)] for patients randomized to receive cobimetinib with vemurafenib compared to those randomized to receive placebo with vemurafenib. The estimated median OS was not reached at the time of the analysis (NR) (95% CI: 20.7, NR) for patients randomized to receive cobimetinib with vemurafenib and 17.0 months (95% CI: 15.0, NR) for the patients randomized to receive placebo with vemurafenib. The ORR was 70% among patients randomized to receive cobimetinib with vemurafenib compared to 50% among patients randomized to receive placebo with vemurafenib ($p < 0.001$). Complete responses were observed in 16% of patients randomized to receive cobimetinib with vemurafenib compared to 10% of patients randomized to receive placebo with vemurafenib. The median duration of response was 13.0 months (95% CI: 11.1, 16.6) among patients randomized to receive cobimetinib with vemurafenib and 9.2 months (95% CI: 7.5, 12.8) among patients randomized to receive placebo with vemurafenib.

7. Safety

The safety of cobimetinib was evaluated primarily in the 247 patients receiving cobimetinib in Study GPO28141; 66% of patients were exposed to cobimetinib for more than 6 months and 24% were exposed to cobimetinib for greater than 1 year. Patients with abnormal liver function tests, history of acute coronary syndrome within 6 months, or evidence of Class II or greater congestive heart failure (New York Heart Association) were not eligible for this trial. The most common adverse reactions in patients receiving cobimetinib and vemurafenib (≥ 20%) were diarrhea, nausea, vomiting, rash, arthralgia, fatigue, photosensitivity reaction, and pyrexia. The most common Grade 3 or 4 laboratory abnormalities were elevations in creatine phosphokinase (13%), GGT (13%), ALT (11%), AST (9%). Fifteen percent of patients discontinued cobimetinib and 55% required dose reductions or interruptions for adverse reactions. The most common adverse reactions resulting in permanent discontinuation were elevation in liver enzymes, rash, pyrexia, and retinal detachment. Among the 247 patients receiving cobimetinib, adverse reactions led to dose interruption or reductions in 55%. The most common reasons for dose interruptions or reductions of cobimetinib were rash (11%), diarrhea (9%), chorioretinopathy, (7%), pyrexia (6%), vomiting (6%), nausea (5%), and increased creatine phosphokinase (CPK) (4.9%). The most serious adverse reactions of cobimetinib, occurring more commonly in the cobimetinib plus vemurafenib arm compared with vemurafenib alone, were an increased risk of second primary basal cell cancers, hemorrhagic events, cardiomyopathy as detected by clinically important decreases in left ventricular ejection fraction, severe skin toxicity, serous retinopathy, rhabdomyolysis, and severe photosensitivity reactions. In addition, the addition of cobimetinib to vemurafenib, decreases but does not eliminate the risk of an increased risk of second primary cutaneous (cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma) and non-cutaneous primary cancers.

8. Advisory Committee Meeting

This NDA was not referred to the Oncologic Drugs Advisory Committee (ODAC) for advice because this drug is not the first in its class, the safety profile is similar to that of other drugs approved for this indication, the clinical trial design is acceptable, and the evaluation of the safety data when used in the treatment of BRAF V600 mutation positive metastatic melanoma did not raise significant safety or efficacy issues that were unexpected in the intended population, and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

9. Pediatrics

On January 31, 2014, Orphan Drug Designation was granted for cobimetinib for Stages IIB, IIC, III and IV melanoma with BRAF V600 mutation. Therefore, this NDA for this proposed indication is exempt from the requirements of the Pediatric Research Equity Act (PREA).

10. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- Risk Benefit Assessment
  Metastatic, BRAF-V600 mutation-positive melanoma is a serious, life-threatening disease with a 5-year survival rate of approximately 16%. The NDA contained the results of an adequate and well-controlled trial that demonstrated a statistically robust and clinically important improvement in OS, PFS, and ORR when cobimetinib was added to vemurafenib, versus vemurafenib alone. The serious risks of cobimetinib, occurring more commonly in the cobimetinib plus vemurafenib arm compared with vemurafenib alone, were an increased risk of second primary basal cell cancers, hemorrhagic events, cardiomyopathy as detected by clinically important decreases in left ventricular ejection fraction, severe skin toxicity, serous retinopathy, rhabdomyolysis, and severe photosensitivity reactions. In addition, the addition of cobimetinib to vemurafenib, decreases but does not eliminate the risk of an increased risk of second primary cutaneous (cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma) and non-cutaneous primary cancers. Dose modifications for adverse reactions were common, with 15% of patients discontinuing cobimetinib for adverse reactions and 55% of patients requiring dose reductions or interruptions for adverse reactions. These adverse reactions are considered acceptable by the patient and medical community, given the incurable nature and low 5-year survival rates.

  Based on the demonstration of the 37% reduction in the immediate risk of death (hazard ratio of 0.63), prolongation in PFS and increased response rate, the benefit of the addition of cobimetinib to vemurafenib outweigh the serious risks of cobimetinib and provide a favorable risk:benefit assessment. Therefore, this application will be approved.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the division and DRISK reviewer that REMS are not required to ensure safe use of cobimetinib and that serious risks of cobimetinib can be mitigated through description of the risks and inclusion of recommended monitoring for and management of these risks. FDA requested that a pharmacovigilance plan be developed and submitted by Genentech to monitor for increased severity of these known risks and to monitor for new safety signals.

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

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

/s/

TAMY E KIM
11/09/2015

RICHARD PAZDUR
11/09/2015