Labeling Supplement – Clinical Review
Division of Oncology 3

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Division/Office	DO3/OOD
Medical Officer	Jamie Brewer, MD
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Product: Established Name (Trade name)	cobimetinib (COTELLIC)
Formulation	Oral
Established Pharmacologic Class (EPC)	Kinase inhibitor
Applicant	Genentech, Inc
Recommended Regulatory Action	Approval

1. Executive Summary

This New Drug Application (NDA) Prior Approval Supplement (PAS) is submitted per the requirements of the Pediatric Written Request- Amendment 1 dated January 19, 2021. This supplemental NDA contains the results from Study GO29665 (Study 1), a Phase I/II multicenter, open-label, single agent, dose-escalation study (NCT02639546), designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of cobimetinib in pediatric and young adult patients aged ≥6 months to <30 years with relapsed/refractory neuroblastoma, embryonal rhabdomyosarcoma, high-grade glioma, low-grade glioma, diffuse intrinsic pontine glioma (DIPG), malignant peripheral nerve sheath tumor, melanoma, rhabdoid tumors (including atypical teratoid/rhabdoid tumor), and high-risk tumors associated with neurofibromatosis or RASopathy (including plexiform neurofibroma and schwannoma).

In addition, this PAS provides for updates to Section 8.4 of the Prescribing Information (PI) to include information regarding the pharmacokinetics observed in the pediatric study (GO29665) and, a request for Pediatric Exclusivity for cobimetinib.

This PAS was reviewed by the clinical Pharmacology review team. Please refer to the Clinical Pharmacology review memo for additional details.

COTELLIC is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

2. Regulatory Background

On November 10, 2015, FDA granted an approval for NDA 216192 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation, in combination with vemurafenib.

A Proposed Pediatric Study Request (PPSR) for cobimetinib was submitted on January 25, 2017, for relapsed or refractory pediatric solid tumors under IND 124530. The original Written Request was issued May 12, 2017, and included a proposal for two studies, a single agent dose escalation study (GO29665; Study 1) and a confirmatory study in selected tumor types (Study 2).

On March 9, 2018, Genentech submitted revisions to the Written Request that clarified the clinical development plan and updated the Written Request with adverse events observed in the pivotal trial. This revised Written Request also included the following clarification:

- the size and the tumor types to be studied in the dose expansion component (Stage 2) of the trial
- stated that an Internal Monitoring Committee (IMC) would review data from the dose escalation component (Stage 1) to select the tumor cohorts for the dose expansion.

There were no changes to the terms of the Written Request and the proposed revisions were determined to be acceptable. FDA issued a revised Written Request on December 11, 2018.

On January 19, 2021, an amendment to the Written Request was issued that removed the requirement for Study 2 due to insufficient antitumor activity in Study 1 (GO29665) to support the additional investigation of cobimetinib as a single agent in pediatric patients with cancer.

3. Review of Clinical Data

Study 1 (GO29665) was an early-phase, multicenter, open-label, single agent, dose-escalation study, designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of cobimetinib in pediatric and young adult patients aged ≥6 months to <30 years with relapsed/refractory neuroblastoma, embryonal rhabdomyosarcoma, high-grade glioma, low-grade glioma, diffuse intrinsic pontine glioma (DIPG), malignant peripheral nerve sheath tumor, melanoma, rhabdoid tumors (including atypical teratoid/rhabdoid tumor), and high-risk tumors associated with neurofibromatosis or RASopathy (including plexiform neurofibroma and schwannoma). The trial had two parts: a dose escalation component to define the recommended phase 2 dose (RP2D) (Stage 1) followed by a disease-specific expansion component in tumors with known or potential RAS/RAF/MEK/ERK pathway activation (Stage 2).

In the dose finding part, cobimetinib once daily at 0.8 mg/kg for the tablet formulation (and 1.0 mg/kg for the suspension formulation) on a 21-day-on/7-day-off (21/7) dosing schedule was identified as the maximum tolerated dose (MTD) for pediatric patients. Cobimetinib steady

state exposures at the MTD were approximately 50% lower compared to exposures at the equivalent dose in adult patients (DLT was ocular toxicity).

Cobimetinib did not show substantial anti-tumor efficacy in pediatric patients in any of the pre-specified indications enrolled to Stage 1 (i.e., high-grade glioma [HGG], low-grade glioma [LGG], malignant peripheral nerve sheath tumor, metastatic mediastinal yolk sac tumor, neuroblastoma, nonrhabdomyosarcoma soft tissue sarcoma, plexiform neurofibroma [PN], and rhabdoid tumor/ATRT), nor in children with LGG enrolled to Stage 2. No new safety signals were observed in pediatric patients and the safety profile generally appeared consistent with the established safety profile of cobimetinib in adults.

4. Labeling Changes

The Applicant's proposed labeling changes consisted of updates to Section 8.4: Pediatric Use. FDA proposed labeling changes are noted with strikethrough deleted text or additions to text in tracked changes format.

(b) (4)

Changes proposed by FDA to Section 8.4 were accepted by the Applicant.

5. Recommended Regulatory Action

No change in the indication for cobimetinib is indicated based on the results of pediatric studies. The clinical review team recommends approval of this sNDA.

The Pediatric Exclusivity Determination Request was reviewed by the FDA Pediatric Exclusivity Review Board and it was determined that the Applicant met the terms of the Written Request. Pediatric Exclusivity has been granted to cobimetinib (Refer to the Pediatric Determination Checklist granted on July 19, 2022) .

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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07/27/2022 03:09:00 PM

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