Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 206192/S-004
Link to EDR	\\CDSESUB1\evsprod\NDA206192\0144
Submission Date	2/11/2022
Submission Type	Pediatric Exclusivity Determination
Brand Name	COTELLIC
Generic Name	Cobimetinib
Dosage Form and Strength	20 mg tablets
Route of Administration	Oral
Proposed Indication	*No new indication is proposed*
Applicant	Genentech, Inc.
Associated IND	IND 124530
OCP Review Team	Lauren Price, PharmD; Jason Moore, PharmD
OCP Final Signatory	Stacy Shord, PharmD, Deputy Division Director, DCPII

1. EXECUTIVE SUMMARY

Cobimetinib is a small-molecule kinase inhibitor currently FDA-approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. The recommended dose is 60 mg orally (PO) once daily (QD) for the first 21 days of each 28-day cycle taken with or without food.

S-004 contains a pediatric exclusivity determination request based on the results of Study GO29665, intended to fulfill FDA's Pediatric Written Request for cobimetinib. Study GO29665 did not achieve the minimum number of responders required for further study of cobimetinib in pediatric patients with solid tumors, and therefore the Applicant does not propose an indication for the treatment of pediatric patients.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 206192/S-004. The supplement has met the terms of the Written Request – Amendment 1 from a clinical pharmacology perspective. Based on the results of Study GO29665, no new indication will be granted. The labeling for cobimetinib was revised to describe the results of Study GO29665 in Section 8.4.

2. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

2.1 Overview of the Product and Regulatory Background

Cobimetinib received FDA approval on November 10, 2015, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. The Applicant submitted a Proposed Pediatric Study Request to FDA on January 25, 2017,

and FDA issued a Written Request on May 12, 2017. This Written Request was subsequently amended and reissued as Written Request – Amendment 1 on January 19, 2021.

The initial Written Request included two planned studies:

- Study 1 (GO29665): A dose escalation and expansion study of cobimetinib in pediatric and young adult patients with pediatric solid tumor types with known or potential RAS/RAF/MEK/ERK pathway activation for which standard therapy has proven to be ineffective (i.e., relapsed or refractory tumors) or intolerable and for whom no curative standard-of-care treatment options exist
- Study 2: Efficacy and safety study in one or more selected tumor types identified on the basis of the results of Study 1

The revised Written Request – Amendment 1 (issued January 19, 2021) removed Study 2. This change was made based on the results of Study GO29665, which did not support conducting further studies of cobimetinib as a single agent in pediatric patients with any of the solid tumors evaluated. The Applicant now submits results of Study GO29665 to fulfill the Written Request – Amendment 1 and request pediatric exclusivity.

2.2 General Pharmacological and Pharmacokinetic Characteristics

The clinical pharmacology of cobimetinib has previously been described in detail in the clinical pharmacology review of the original NDA 206192 submission. Refer to the original NDA Clinical Pharmacology Review for a detailed description of the clinical pharmacology data. Briefly, cobimetinib is orally bioavailable with T_{max} approximately 2.4 hrs after administration. In adult patients with cancer administered the recommended dosage of 60 mg PO QD, the geometric mean steady-state $AUC_{0\text{-}24h}$ was 4,340 ng*h/mL (61% CV) and C_{max} was 273 ng/mL (60% CV).

2.3 Clinical Pharmacology Questions

2.3.1 Do the results of Study GO29665 fulfill the Written Request – Amendment 1 from a clinical pharmacology perspective?

Study ID and Title: **Study GO29665** – A Phase I/II, Multicenter, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of Cobimetinib in Pediatric and Young Adult Patients with Previously Treated Solid Tumors (iMATRIX Cobi)

Design and Enrollment: Study GO29665 is an open-label, dose-escalation study of cobimetinib in pediatric and adult patients with previously treated solid tumors. Separate cohorts enrolled patients treated with the approved tablet formulation and an investigational suspension formulation. Cobimetinib was administered daily on Days 1-21 of each 28-day cycle. A total of 56 patients were enrolled; see **Table 1** for enrollment summary by phase, formulation, dose, and age. Refer to the Clinical review for additional details.

Table 1: Study GO29665 Enrollment Summary

Phase	Formulation	Dose	Age Group				*Total*
			2 to <6 years	6 to <12 years	12 to <17 years	≥17 years	
1	Tablet	0.6 mg/kg	-	3	3	-	*6*
		0.8 mg/kg	-	4	2	-	*6*
		1 mg/kg	-	5	1	-	*6*
	Suspension	0.6 mg/kg	-	6	-	-	*6*
		0.8 mg/kg	2	3	2*	-	*7*
		1 mg/kg	1	5	2	-	*8*
		1.33 mg/kg	-	3	2	-	*5*
2	Suspension	1 mg/kg	5	4	2	1	*12*
Total	*Any*	*Any*	*8*	*33*	*14*	*1*	*56*

*1 patient with incomplete birth date information was considered a pediatric patient (<17 years) for analyses

Source: Study GO29665 ADSL dataset

Results:

Safety/Dose-Limiting Toxicity (DLT) Summary: During dose escalation, DLTs occurred in 6 patients — 2 patients treated with 1 mg/kg tablet formulation, 1 patient treated with 0.6 mg/kg suspension formulation, and 3 patients treated with 1.33 mg/kg suspension formulation. Five of the DLTs were ocular toxicities (chorioretinopathy, retinal detachment, serous retinal detachment, and detachment of retinal pigment epithelium). Ocular toxicities, including serous retinopathy and retinal vein occlusion, were previously observed in adult patients receiving cobimetinib. The maximum tolerated dose (MTD) was defined per protocol as 0.8 mg/kg with the tablet formulation and 1 mg/kg with the suspension formulation. An expansion cohort subsequently enrolled 12 patients treated with 1 mg/kg suspension formulation. Refer to the Clinical review for additional details.

Efficacy Summary: Three patients (all with low-grade glioma) had a partial response (5.4%); there were no other responses. The planned response assessment stage was not completed given that the pre-specified minimum number of responders for a tumor-type cohort expansion was not met. Refer to the Clinical review for additional details.

Pharmacokinetics (PK): PK samples were collected from all 56 patients on Day 1 and from 53 patients at steady state. On both sampling days, blood samples were collected pre-dose and 2, 4, 6, and 24 hrs post-dose. Samples were analyzed using validated bioanalytical methods (refer to Appendix) and PK parameters were calculated using non-compartmental analysis. A summary of C_{max} and $AUC_{0\text{-}24h}$ in pediatric patients in Study GO29665 is presented in **Table 2**.

Table 2: Cobimetinib Pharmacokinetic Parameters in Pediatric Patients with Solid Tumors

Phase	Formulation	Dose	Day 1		Steady-State	
			C_{max}	AUC_{0-24h}	C_{max}	AUC_{0-24h}
1	Tablet	0.6 mg/kg	62.0 (70%)	868 (79%)	54.5 (45%)	829 (62%)
		0.8 mg/kg	88.3 (89%)	1,004 (83%)	181 (84%)	2,803 (74%)
		1 mg/kg	144 (40%)	1,431 (38%)	193 (34%)	2,330 (35%)
	Suspension	0.6 mg/kg	51.5 (81%)	741 (76%)	122 (77%)	1,736 (79%)
		0.8 mg/kg	67.4 (130%)	1,100 (92%)	156 (65%)	1,767 (76%)
		1 mg/kg	136 (56%)	1,602 (52%)	157 (89%)	2,159 (88%)
		1.33 mg/kg	111 (39%)	1,558 (35%)	222 (51%)	3,450 (66%)
2	Suspension	1 mg/kg	44.5 (72%)	598 (70%)	124 (44%)	1,519 (64%)
1 & 2	Suspension	1 mg/kg	73.6 (84%)	932 (76%)	136 (80%)	1,720 (82%)

Notes: Parameters presented as geometric mean (CV%). One adult patient was excluded from the analysis. Additional patients were excluded if there were insufficient samples to calculate PK parameters or resulting PK parameters were outliers (>3 standard deviations from mean).

Source: Reviewer's Analysis of Study GO29665 ADPC dataset

Conclusions: The pharmacokinetics of cobimetinib in pediatric patients was adequately assessed. In adult patients treated with the approved recommended dosage (60 mg PO QD), the geometric mean steady-state C_{max} was 273 ng/mL and AUC_{0-24h} was 4,340 ng*h/mL. Compared with exposure in adult patients treated with the approved recommended dosage, both the steady-state C_{max} and AUC_{0-24h} of cobimetinib were lower in pediatric patients treated at the MTD with either the tablet formulation (0.8 mg/kg) or the investigational suspension formulation (1 mg/kg); see grey highlighted boxes in **Table 2**. Higher doses of cobimetinib could not be achieved in pediatric patients due to the observed toxicities and DLTs. Given the lack of significant activity in pediatric patients with solid tumors, no new indication will be granted and the Applicant will not market the suspension formulation at this time.

Written Request Clinical Pharmacology Components:

- Age and number of patients to be studied:
  - Per the Written Request – Amendment 1, approximately 20-50 patients age ≥6 months to <18 years (Stage 1) or ≥6 months to <30 years (Stage 2) were to be enrolled.
  - Study GO29665 enrolled a total of 56 patients ranging in age from 3 years to 29 years. This enrollment meets the criteria of the Written Request – Amendment 1.
- Pharmacokinetic endpoints:
  - Per the Written Request – Amendment 1, cobimetinib C_{max} and AUC_{0-24h} after single dose and multiple dose administration were to be evaluated.
  - PK samples were collected from all patients enrolled in Study GO29665 and PK parameters (including C_{max} and AUC_{0-24h}) were calculated after the first dose (Day 1) and at steady state. This evaluation meets the criteria of the Written Request – Amendment 1.
- Drug formulation:
  - Per the Written Request – Amendment 1, two formulations (20 mg tablets and a to-be-determined suspension formulation) were to be used in the pediatric study. The Written Request – Amendment 1 includes language directing the Applicant to market an age-appropriate formulation if it is found to be safe and effective in pediatric patients.

- Study GO29665 utilized both 20 mg tablets and an investigational suspension formulation. Given that efficacy and safety were not demonstrated in pediatric patients with solid tumors, the suspension formulation will not be marketed at this time. The drug formulation usage meets the criteria of the Written Request – Amendment 1.

2.4 Outstanding Issues

None.

2.5 Summary of Labeling Recommendations

Section 8.4 was revised as follows:

Previous Language	The safety and effectiveness of COTELLIC have not been established in pediatric patients. *Juvenile Animal Data* In a 4-week juvenile rat toxicology study, daily oral doses of 3 mg/kg (approximately 0.13–0.5 times the adult human AUC at the recommended dose of 60 mg) between postnatal Days 10–17 (approximately equivalent to ages 1–2 years in humans) were associated with mortality, the cause of which was not defined.
New Language	The safety and effectiveness of COTELLIC have not been established in pediatric patients. The safety and effectiveness of cobimetinib were assessed, but not established, in a multi-center, open-label, dose-escalation study in 55 pediatric patients aged 2 to 17 years with solid tumors [NCT02639546]. No new safety signals were observed in pediatric patients in this trial. Exposure in pediatric patients who received cobimetinib at the maximum tolerated dosage were lower than those previously observed in adults who received the approved recommended dosage. *Juvenile Animal Data* In a 4-week juvenile rat toxicology study, daily oral doses of 3 mg/kg (approximately 0.13–0.5 times the adult human AUC at the recommended dose of 60 mg) between postnatal Days 10–17 (approximately equivalent to ages 1–2 years in humans) were associated with mortality, the cause of which was not defined.
Rationale for Changes	Based on the results of Study GO29665, no new indication for the treatment of pediatric patients is warranted. The Pediatric Use section of the labeling was revised to reflect the results of Study GO29665 including the reduced cobimetinib exposure in pediatric patients relative to adults.

3. APPENDIX

3.1 Summary of Bioanalytical Method Validation and Performance

Validated bioanalytical methods were used to measure concentrations of cobimetinib in plasma from Study GO29665 (Method G73HPP; supported-liquid extraction followed by analysis using LC-MS/MS). The method validation and in-study performance for plasma samples was acceptable based on the current Bioanalytical Method Validation Draft FDA Guidance for Industry. Refer to the original NDA 206192 Clinical Pharmacology review for previous review of the analytical method validation.

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