CLINICAL PHARMACOLOGY REVIEW

NDA	022580, Sequence 0590, Supplement 021
Submission Date	August 25, 2021
Brand Name	QSYMIA
Generic Names	Phentermine and topiramate
Reviewer	S. W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Lin Zhou, Ph.D.
Pharmacometrics Reviewer	Jiajun Liu, Pharm.D., MSc.
Pharmacometrics Team Leader	Justin Earp, Ph.D.
OCP Division	Cardiometabolic and Endocrine Pharmacology
OND Division	Diabetes, Lipid Disorders, and Obesity
Sponsor	VIVUS LLC
Formulation; Strength	Phentermine HCl immediate release and topiramate extended release fixed dose combination oral capsules; 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg
Submission Type	Standard submission
EDR Link	\\CDSESUB1\evsprod\NDA022580\0590
Relevant IND	(b) (4)
Indication	Treatment of obesity, including weight loss and maintenance of weight loss together with diet and exercise

Background

Qsymia is a fixed-dose combination of proprietary formulations of phentermine and extended-release topiramate, approved for the chronic weight management in overweight and obese adults [available in four fixed-dose strengths: low (3.75 mg phentermine/23 mg ER topiramate), mid (7.5 mg/46 mg), three quarter (11.25 mg/69 mg), and high dose (15 mg/92 mg)]. Qsymia was approved on July 17, 2012.

The purpose of the supplement is to update the label using data from the final report for PMR 1901-2 (Study OB-403: *A Phase IV, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Determine the Safety and Efficacy of VI-0521 in Obese Adolescents*) that Qsymia is indicated in adolescents 12 to 17 years of age inclusively with body mass index (BMI) in the 95th percentile or greater standardized for age and gender.

The QSYMIA capsules evaluated in pivotal Study OB-403 are identical to the commercially marketed QSYMIA capsules. No pharmacokinetic data was collected in Study OB-403.

However, the Sponsor conducted a pharmacokinetic study in obese adolescents for QSYMIA (Study OB-402 for PMR 1901-1 titled "*A Randomized, Double-Blind, Placebo-Controlled, Pharmacokinetic and Pharmacodynamic Study of VI-0521 in Obese Adolescents*") to find the dose for Study OB-403.

US Labeling Update

With the addition of the efficacy and safety information for adolescents 12-17 years of age, the Qsymia US label was also revised to include an additional sub-heading in Section 12.3 *Pharmacokinetics* with the following language:

Pediatric Patients 12 (b) (4)

A randomized, double-blind, placebo-controlled study was conducted to evaluate the population pharmacokinetics of Qsymia using data from 37 pediatric patients (12 to 17 years of age, (b) (4) *) with obesity. Qsymia dosages of 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg were studied. Qsymia exposure in the pediatric patients appeared comparable to that in adults.*

In addition, information presented in Section 7. DRUG INTERACTIONS was reformatted to be consistent with the current labeling practice.

Recommendation

The Office of Clinical Pharmacology has reviewed the submitted datasets, reports, and reached agreement on the revised Qsymia label and indications. PMR 1901-2 has been fulfilled.

Pharmacometric Review

The aim of the pharmacometric review was to incorporate pediatric PK information in the label given the new efficacy and safety data for adolescents. The pediatric PK data and population PK model were reviewed previously by Dr. Jing Niu (dated May 31, 2017; reference ID: 4105346) but not incorporated in the label with that submission. Dr. Niu's review included exposure-matching considerations (to adults) for dose-finding in adolescents utilizing results from a population PK analysis with data from Study OB-402. In this submission, the reviewer identified PK characteristics from Dr. Niu's review that would be relevant to labeling the pharmacokinetics of phentermine and topiramate. No changes to the population PK model or PK data were made in this submission and no additional pharmacokinetic data were collected in the pivotal pediatric trial (Study OB-403).

A summary of our previous findings is described in brief. The pharmacokinetic profile of Qsymia was assessed for doses of 3.75 mg/23 mg (low-dose), 7.5 mg/46 mg (mid-dose), and 15 mg/92 mg (top-dose) in obese pediatric patients between 12 to 17 years of age, inclusively. For phentermine, the distributions of AUC [minimum, maximum (ng·h/mL)] and C_{max} [minimum, maximum (ng/mL)] were comparable between pediatric patients and adults for low-dose (AUC, 350-1300 vs. 220-4100; C_{max}, 20-62 vs. 11-180, respectively), mid-dose (AUC, 510-1800 vs. 480-4000; C_{max}, 34-95 vs. 26-180, respectively), and top-dose (AUC,1400-5700 vs. 820-6000; C_{max}, 62-180 vs. 48-280, respectively). For topiramate, the distributions of AUC [minimum, maximum (ng·h/mL)] and C_{max} [minimum, maximum (ng/mL)] were comparable between

pediatric patients and adults for low-dose (AUC, 12-38 vs. 9.4-52; C_{max}, 0.58-1.18 vs. 0.44-2.5, respectively), mid-dose (AUC, 17-71 vs. 28-110; C_{max}, 0.88-3.3 vs. 1.3-5.4, respectively), and top-dose (AUC, 40-120 vs. 41-190; C_{max}, 2.0-5.6 vs. 2.0-9.0, respectively).

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