CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22580Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 16, 2012
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	22580
Applicant Name	Vivus Pharmaceuticals
Date of Re-Submission	October 17, 2011
PDUFA Goal Date	July 17, 2012
Proprietary Name /Established Name	Phentermine+Extended-Release Topiramate/Qsymia
Dosage Forms / Strength	Fixed-dose combination capsules of 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg
Proposed Indication	Chronic Weight Management
Recommended Action	Approve

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Mary Roberts, MD
Statistical Review	Lee Pian, PhD/Benjamin Neustifter, PhD
Deputy Director for Safety	Amy Egan, MD, MPH
Pharmacology/Toxicology Review	David Carlson, PhD
CMC Review/OBP Review	Joseph Leginus, PhD
Clinical Pharmacology Review	Johnny Lau, PhD
DDMAC	Samuel Skariah, RPh
OSI	Xikui Chen, PhD/Susan Leibenhaut, MD
OSE/DMEPA	Lissa Owens, PharmD/Kevin Wright, PharmD
OSE/DEPI	Julia Ju, PharmD, PhD
OSE/DRISK	Joyce Weaver, PharmD
Thorough QT Consult	Joanne Zhang, PhD
Controlled Substance Staff	Chad Reissig, PhD
PMHS	Jeanine Best, RN, PNP
SEALD	Ann Marie Trentacosti, MD
OND/DPP	Sonia Tabacova, MD, PhD
OND/DRUP	Gerald Willett, MD
OND/DAIOP	Wiley A. Chambers, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DEPI=Division of Epidemiology
DRISK=Division of Risk Management
PMHS=Pediatric and Maternal Health Staff
SEALD=Study Endpoints and Labeling Development team
DPP=Division of Psychiatry Products
DRUP=Division of Reproductive and Urological Products
DAIOP=Division of Anti-Infective and Ophthalmologic Products

1. Introduction and Background

This is the second review cycle for the Qsymia application.

Qsymia is a fixed-dose combination of phentermine and extended-release topiramate for which the applicant is seeking approval for weight management in obese (BMI $\geq$ 30 kg/m^2) and overweight (BMI 27-29.9 kg/m^2) individuals when accompanied by at least one weight-related comorbidity. Three dose levels were studied in the clinical development program: 3.75/23 mg (low), 7.5/46 mg (mid), and 15/92 mg (high). The mid dose of Qsymia is proposed as the maintenance dose.

Phentermine, a sympathomimetic, was approved in 1959 for the treatment of obesity. Since 1973 it has been indicated for short-term use only. Topiramate, an inhibitor of carbonic anhydrase, was approved in 1996 for the treatment of seizures and gained approval for the prevention of migraine headache in 2004. The approved doses for phentermine are up to 37.5 mg/day. The approved doses for topiramate are up to 400 mg/day for seizures and up to 100 mg/day for migraine prophylaxis.

The Qsymia application was initially submitted to the Division on 28 December 2009. The long-term efficacy and safety of the three proposed Qsymia doses were assessed in two phase 3 clinical trials referred to as OB-302 and OB-303. Approximately 3500 overweight and obese individuals, many with weight-related comorbidities such as hypertension and dyslipidemia, were treated with placebo or low, mid, or high doses of Qsymia for up to one year in studies OB-302 and OB-303.

As discussed in greater detail in section 6 of this memorandum, the mid and high doses of Qsymia satisfied both of the Agency's weight-loss efficacy criteria (5% mean and categorical), while the low dose satisfied the categorical efficacy criterion.

The efficacy and safety of Qsymia were discussed at a 15 July 2010 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting. When asked if they believed that the potential benefits of the drug outweighed its potential risks, 10 committee members voted "no" and six voted "yes." Teratogenicity, in particular, oral clefts, and elevations in heart rate were specific safety concerns raised by the committee members who voted against regulatory approval.

On 28 October 2010, the Division issued a Complete Response Letter (CRL) to the applicant. The CRL read in part:

1. Topiramate, one of the components of phentermine/topiramate, is teratogenic in several animal species and preliminary data from the North American Antiepileptic Drug Pregnancy Registry raise concern that it poses teratogenic risk to women of child-bearing potential (WOCBP). Despite multiple strategies to prevent pregnancy, women did become pregnant during participation in the phentermine/topiramate clinical development program.

a. Provide a comprehensive assessment of topiramate's and phentermine/topiramate's teratogenic potential.
b. Provide a detailed plan and strategy to evaluate and mitigate the potential risk for teratogenicity or fetal harm in WOCBP taking phentermine/topiramate for the treatment of obesity.

2. A larger percentage of subjects treated with phentermine/topiramate compared with placebo developed increases in heart rate.

Provide evidence that the elevations in heart rate associated with phentermine/topiramate do not increase the risk for major adverse cardiovascular events.

The applicant submitted a complete response on 17 October 2011. The complete response included data from three observational studies examining the effect of topiramate on risk for fetal malformations, analyses of Qsymia's effect on blood pressure, heart rate, and adverse cardiovascular events, and the final study report for the long-term extension study OB-305.

This memorandum summarizes the principal review disciplines' evaluations of the data submitted in the applicant's complete response. Where appropriate, I also reiterate data and analyses provided in my complete response memorandum.

2. CMC

The CMC reviewer states that there are no pending deficiencies and recommends that the application be approved.

3. Nonclinical Pharmacology/Toxicology

Prior to the study of Qsymia in obese pediatric subjects, Dr. Carlson, the primary pharmacology/toxicology reviewer, recommends that the applicant perform studies in juvenile animals to assess the effects of Qsymia on behavior, learning, and memory. I agree with this recommendation.

Contingent upon a category X pregnancy designation, Dr. Carlson recommends approval of the application.

4. Clinical Pharmacology

Based on review of a thorough QT study, the Agency's interdisciplinary review team for QT studies concluded that Qsymia does not significantly prolong the QT interval. The largest upper bounds of the 2-sided 90% confidence interval for the mean difference between Qsymia (7.5/46 mg and 22.5/138 mg) and placebo were below 10 milliseconds.

High-dose Qsymia decreased ethinyl estradiol AUC by 16% and increased norethindrone C_{max} and AUC by 22% and 16%, respectively, in a drug-drug interaction study with an oral

contraceptive. Because the effectiveness of oral contraceptives is due to the levels of norethindrone, these drug-drug interaction data do not raise concern that Qsymia will reduce the contraceptive effectiveness of ethinyl estradiol and norethindrone-based oral contraceptives. This viewpoint was reiterated by Dr. Gerald Willett, medical officer from the Division of Reproductive and Urologic Products, in a consult to the Division dated 23 April 2012.

The approved labeling for topiramate (Topamax®) indicates that the drug can cause an increase in serum creatinine. The exact mechanism is unknown. Dr. Mary Roberts, the primary clinical reviewer, noted in her review of the clinical data that subjects randomized to Qsymia did indeed have a small mean increase in serum creatinine relative to subjects randomized to placebo. Although the applicant believes that this increase is due in part to topiramate's inhibition of hOAT3 and hOCT1 transporters in the kidney, Dr. Lau, the primary clinical pharmacology reviewer, was unable to confirm this assertion because the applicant relied on a redacted review from the Japanese regulatory authority. The review did not provide any details regarding experimental methods.

Thus, Dr. Lau recommends that the applicant conduct the appropriate *in-vitro* studies to assess whether topiramate's action to increase serum creatinine is secondary to inhibition of renal transporters of creatinine. I agree with this recommendation. The studies will be conducted as post-marketing requirements.

Dr. Lau concludes that the clinical pharmacology data submitted in support of the application are acceptable and recommends approval.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

As outlined in the Agency's 2007 draft guidance for weight management products, efficacy can be established by satisfying one of two criteria:

1. Mean: The mean percent weight loss in the active drug group is at least 5% greater than that in the placebo group and the difference between groups is statistically significant.
2. Categorical: The proportion of subjects in the active drug group who lose at least 5% of baseline weight is at least 35%, approximately double the proportion in the placebo group, and the difference between groups is statistically significant.

As shown in the below tables excerpted from Dr. Robert's review, the mid and high doses of Qsymia satisfied both the mean and categorical criteria, whereas the low dose only satisfied the categorical criterion.

Mean Percent Weight Loss from Baseline to One Year (LOCF)

Pooled Data from Studies OB-302 OB-303	Treatment Group	N	Mean Percent Weight Loss	LS Mean Difference from Placebo	95% CI	p-value
	Placebo	1477	-1.7	--	--	--
	Low	234	-5.1	-3.2	(2.1, 4.3)	<0.0001
	Mid	488	-8.4	-6.7	(6.0, 7.5)	<0.001
	High	1479	-10.6	-8.9	(8.3, 9.4)	<0.0001

Proportion of Subjects Losing ≥ 5% of Baseline Body Weight (LOCF)

Pooled Data from Studies OB-302 OB-303	Treatment Group	Frequency	Placebo-Subtracted Difference
	Placebo	19.6%	--
	Low	44.9%**	25.3
	Mid	62.1%**	42.5
	High	68.9%**	49.3

**p<0.0001

With the exception of heart rate, relative to placebo, treatment with mid and high doses of Qsymia was associated with numerical improvement in common weight-related comorbidities such as blood pressure, levels of triglycerides, high density lipoprotein lipid cholesterol (HDL-C), low density lipoprotein lipid cholesterol (LDL-C), and measures of glycemia. Treatment with Qsymia was associated with the initiation of fewer anti-hypertensive medications.

In a subgroup of subjects who had type 2 diabetes at baseline, treatment with the mid and high doses of Qsymia led to a -0.3% placebo-subtracted reduction in HbA1c levels in both active treatment groups. Moreover, fewer patients treated with Qsymia required the initiation of new anti-diabetic medications.

The incidence of newly-diagnosed type 2 diabetes during the one-year treatment period was reduced by 37% in the mid-dose Qsymia group and by 46% in the high-dose Qsymia group.

In sum, all three doses of Qsymia satisfy the Agency's weight-loss efficacy criteria.

The applicant included the final study report for study OB-305 in their complete response. This was a one-year extension of non-randomly selected patients who took part in the one-year, randomized, placebo-controlled study OB-303. Given that the data from study OB-305 are from a non-randomized sample of patients, I agree with the Agency statisticians that they are observational in nature and contribute little to the placebo-controlled one-year data[1].

7. Safety

[1] In my complete response memorandum, I questioned whether the benefit-risk profile of mid-dose Qsymia was more favorable than high-dose Qsymia. I noted that the two-year data from study OB-305 would be informative in this regard. Given the observational nature of these data, upon reconsideration, I do not believe that they provide useful information with respect to the benefit-risk assessment of high-dose Qsymia relative to mid-dose Qsymia. The benefit-risk profile of high-dose Qsymia supports approval.

The CRL identified teratogenicity, increases in heart rate, and the lack of an adequate risk evaluation and mitigation strategy (REMS) as deficiencies that needed to be adequately address before regulatory approval would be considered.

Teratogenicity

Topiramate, at clinically relevant doses, increases the incidence of fetal malformations, including craniofacial defects, in several animal species. Because of concern about teratogenicity, the clinical development program for Qsymia required that all women of child-bearing potential (WOCBP) have a negative pregnancy test each month and agree to use two forms of birth control. As discussed in Dr. Roberts' review, there were 34 pregnancies in the Qsymia development program. Following the 12th pregnancy, the applicant initiated the following additional risk minimization strategies: all WOCBP were re-consented and all investigator sites were trained to counsel these women at every study visit. These additional measures to reduce the risk of pregnancy appeared to have worked, as the rate of pregnancies decreased by about 65% following their implementation. There were no major congenital malformations (MCM) reported for the 19 of 34 pregnancies carried to term.

Preliminary data made available in 2010 from the North American Antiepileptic Drug Pregnancy Registry suggested that topiramate increased the risk for oral clefts (OC) (OR=9.6, 95% CI, 3.6, 25.7). Based on these data and concern expressed about teratogenicity at the July 2010 EMDAC meeting, the applicant submitted, in their complete response, new data regarding teratogenicity from two observational studies which they funded. These are the Wolters Kluwer study and the Fetal Outcomes Retrospective Topiramate Exposure Study (FORTRESS). Additional topiramate teratogenicity data come from an observational study conducted by the Centers for Disease Control (CDC) and the Slone Epidemiology Center at Boston University (hereafter, the CDC/Slone study).

The data from the Wolters Kluwer and FORTRESS studies have been reviewed in detail by Dr. Julia Ju from the Office of Surveillance and Epidemiology. Data from the CDC/Slone study were only available in abstract form but the results were presented by a co-investigator of the study at the 22 February 2012, EMDAC meeting held for Qsymia.

The Wolters Kluwer study was a retrospective cohort study that used data from (b) (6) (b) (6) patient longitudinal datasets covering the years 2003 to 2010. The study objective was to examine the risk of MCMs and OCs among infants exposed to topiramate in utero compared with controls. The two exposure cohorts were infants exposed to topiramate in utero anytime during pregnancy (N=910) and infants exposed to topiramate in utero during the first trimester (n=870). Five control cohorts were used and defined as follows:

- Women exposed to other antiepileptic drugs during the first trimester of pregnancy (n=3,165)
- Women with a diagnosis of epilepsy but without topiramate exposure (n=2,607)
- Women with a diagnosis of migraine but no diagnosis of epilepsy and not treated during pregnancy with acute or preventive migraine drugs (n=26,865)

- Women with a diagnosis of migraine but no diagnosis of epilepsy and treated during pregnancy with acute and preventive migraine drugs (n=2,526)
- Women with a diagnosis of diabetes other than gestational (13, 063)

FORTRESS was a retrospective cohort study that included four data sources (HealthCore, OptumInsight, Kaiser Northern California, and Thomas Reuters). The primary objectives were to estimate the prevalence ratios of OCs and MCMs in newborns of women exposed to topiramate during the first trimester of pregnancy when compared with (a) the formerly exposed (FE) cohort: newborns of women with remote prior exposure (at least 120 days prior to the index pregnancy) to topiramate or another antiepileptic, and (b) the similar medical profile (SMP) cohort: newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester topiramate exposure.

The topiramate-exposed cohort was composed of 1,945 subjects; the FE cohort was composed of 13, 512 subjects; and the SMP was composed of 13, 614 subjects. Because the reported results have not been validated, the study is considered preliminary.

The CDC/Slone study was a pooled case-control study that used data from two databases to identify women whose babies had birth defects (cases) (n=3,034 OC and 33,605 MCM) and women whose babies did not have birth defects and gave birth in the same area during the same years (controls) (n=15,367) as the cases.

As shown in the below table taken from Dr. Roberts' review, the point estimates for risk of OCs from the three observational studies range from 1.5 to 5.4. The estimate of risk for OCs reached nominal statistical significance in the CDC/Slone study only. The point estimates for risk of MCM in the Wolters Kluwer and CDC/Slone studies were near unity, with 95% confidence intervals that crossed one.

It is reassuring that the Slone/CDC study did not report an increase in risk for MCMs.

Final data on risk for MCM from FORTRESS are expected in approximately one year. I do not believe that it is necessary to wait for these data, as the current body of evidence is sufficient to make an assessment of topiramate's teratogenic risk and how it affects Qsymia's benefit-risk profile.

Summary of Studies Evaluating the Teratogenic Risk Associated with Topiramate

Study	**Cohorts compared**	**Oral clefts**		**Major congenital malformations**	
Wolters Kluwer	Topiramate (mono and poly therapy) vs Migraine no meds	Estimated association[1]	95% CI	Estimated association[1]	95% CI
		1.47	0.36 – 6.06	1.12	0.81 – 1.55
FORTRESS	Topiramate monotherapy vs Formerly exposed to AED	2.00	0.71 – 5.68.	Pending	Pending
CDC/Slone	Topiramate monotherapy vs no	5.36	1.49 – 20.07	1.01	0.37 – 3.22

	AED				
1Wolters Kluwer: unadjusted relative risk, FORTRESS prevalence ratio, CDC/Slone odds ratio					

As noted in her consults to the Division and in her presentation at the 22 February 2012 EMDAC meeting, Julie Ju, an epidemiologist from the Office of Surveillance and Epidemiology, stressed that there are limitations and potential biases applicable to each observational study. Of note, because of over-estimation of drug exposure, use of a composite OC measure, lack of case validation, and misclassification of first trimester of pregnancy, the Wolters Kluwer and FORTRESS data are susceptible to underestimation of the risks of OCs and MCMs. Due to possible recall bias, the CDC/Slone data may overestimate the risks for OCs and MCMs.

I believe that Dr. Ju drew reasonable conclusions from her review of the observational data on topiramate and risk for OCs and MCMs. These were: 1) there is no evidence for an increased risk of overall MCMs with topiramate exposure; 2) first trimester topiramate exposure is associated with an increased risk of OCs; and 3) the estimate relative risks of OCs were unstable, but could range from 2 fold up to 5 fold based on the currently available point estimates.

Given that the current data suggest that topiramate, at the doses present in Qsymia, increases the risk for OCs and that many of the patients likely to use a weight management drug are WOCBP, there is ample justification to require a REMS to ensure that the benefits of Qsymia outweigh the potential teratogenic risk. The details of the Qsymia REMS are covered in section 10 below.

Heart Rate and Blood Pressure

Some members of the July 2010 EMDAC raised concern about Qsymia's effect on heart rate and its effect on risk for cardiovascular disease. For this reason, the CRL requested that the applicant provide evidence that increases in heart rate do not increase the risk for major adverse cardiovascular events. To gain a fuller appreciation of the data regarding heart rate, one needs to also consider the changes in blood pressure and rate-pressure product associated with Qsymia.

As depicted in the below table from Dr. Roberts' review, the mid and high doses of Qsymia were associated with nominally significant reductions in mean systolic and diastolic blood pressures compared with placebo. There was a non-significant reduction in systolic blood pressure in the low-dose Qsymia group in comparison to the placebo group. There was a non-significant increase in diastolic blood pressure in the low-dose Qsymia group in comparison to the placebo group.

While there was no change in heart rate from baseline to Year 1 in the placebo group, the mean changes in the low, mid, and high-dose Qsymia groups were 1.3 bpm, 0.6 bpm, and 1.6 bpm, respectively (Table below). Compared with placebo, the mean increase in heart rate in the high-dose Qsymia was of nominal statistical significance.

Mean Changes in Blood Pressure and Heart Rate from Baseline to Year 1

	Placebo	Qsymia Low	Qsymia Mid	Qsymia High
Number of subjects with baseline and endpoint measurements	n=1532	n=234	n=488	n=1553
Systolic blood pressure (mmHg)				
Baseline mean (SD)	126.5 (13.25)	122.5 (11.11)	128.5 (13.63)	125.7 (13.12)
Mean change (SD)	-2.1 (14.01)	-3.3 (11.95)	-5.2 (14.77)	-5.2 (14.48)
Comparison to placebo p-value		0.2322	<0.0001	<0.0001
Diastolic blood pressure (mmHg)				
Baseline mean (SD)	79.6 (8.95)	77.8 (7.49)	80.6 (8.71)	79.0 (8.76)
Mean change (SD)	-1.9 (9.61)	-0.9 (8.29)	-3.3 (9.87)	-2.9 (9.40)
Comparison to placebo p-value		0.1362	0.0044	0.0023
Heart rate (bpm)				
Baseline mean (SD)	72.5 (9.58)	72.3 (9.22)	72.2 (10.07)	72.7 (9.87)
Mean change (SD)	0 (10.19)	1.3 (10.32)	0.6 (10.18)	1.6 (10.28)
Comparison to placebo p-value		0.0688	0.2933	<0.0001

In addition to mean changes in blood pressure and heart rate, it is instructive to evaluate categorical changes in these parameters. These data are shown in the following table from Dr. Roberts' review.

Categorical Increases in Blood Pressure and Heart Rate from Baseline to any Time during Year 1

	Placebo N=1561 n (%)	Qsymia Low N=240 n (%)	Qsymia Mid N=498 N (%)	Qsymia High N=1580 n (%)
Systolic blood pressure				
>5 mmHg	1033 (66.2)	141 (58.8)	289 (58.0)	923 (58.4)
>10 mmHg	733 (47.0)	101 (42.1)	182 (36.5)	645 (40.8)
>15 mmHg	506 (32.4)	71 (29.6)	132 (26.5)	436 (27.6)
>20 mmHg	295 (18.9)	29 (12.1)	79 (15.9)	235 (14.9)
>25 mmHg	180 (11.5)	16 (6.7)	49 (9.8)	134 (8.5)
>30 mmHg	86 (5.5)	9 (3.8)	26 (5.2)	63 (4.0)
Diastolic blood pressure				
>5 mmHg	891 (57.1)	141 (58.8)	280 (56.2)	855 (54.1)
>10 mmHg	465 (29.8)	76 (31.7)	147 (29.5)	469 (29.7)
>15 mmHg	247 (15.8)	35 (14.6)	63 (12.7)	234 (14.8)
>20 mmHg	100 (6.4)	10 (4.2)	27 (5.4)	81 (5.1)
Heart rate				
>5 bpm	1021 (65.4)	168 (70.0)	372 (74.7)	1228 (77.7)
>10 bpm	657 (42.1)	120 (50.0)	251 (50.4)	887 (56.1)
>15 bpm	410 (26.3)	79 (32.9)	165 (33.1)	590 (37.3)
>20 bpm	186 (11.9)	36 (15.0)	67 (13.5)	309 (19.6)

The proportions of subjects treated with Qsymia who developed categorical increases in blood pressure were, in general, numerically lower compared with placebo. In contrast, the proportions of subjects treated with Qsymia who developed categorical increases in heart rate were numerically larger compared with placebo. There appeared to be a dose response between the low and mid doses versus the high dose of Qsymia.

Examining the rate-pressure product (heart rate x systolic blood pressure), considered by some to be an index of myocardial oxygen demand, is instructive in the case of Qsymia given that the drug lowers blood pressure to a greater extent than it increases heart rate.

Compared with a 0.13 reduction in mean rate-pressure product (RPP) from baseline to Year 1 in the placebo group, the mean reductions in the RPP in the low-, mid-, and high-dose Qsymia groups were 0.19, 0.23, and 0.18, respectively. The differences between placebo and the Qsymia groups were not statistically significant.

In the subgroup of heart rate outliers, defined as those with an increase in heart rate > 10 bpm over baseline at two or more consecutive visits or a heart rate > 90 bpm at two or more consecutive visits, the mean increase in RPP from baseline to Year 1 was 0.83 in the placebo group versus 0.69, 0.54, and 0.55 in the Qsymia low, mid, and high-dose groups. Compared with placebo, the numerically smaller change in RPP in the Qsymia high-dose group was of nominal statistical significance.

While mindful of the limitations of post-hoc subgroup analyses, the RPP data are somewhat reassuring since they suggest that, on average, myocardial oxygen demand is not increased with Qsymia versus placebo treatment.

The applicant's complete response included data from a phase 2 clinical study designed to examine the effect of Qsymia in patients with obstructive sleep apnea. Polysomnograms provided an automated measure of heart rate during sleep in patients treated with Qsymia and placebo.

Briefly, 45 obese adults with obstructive sleep apnea were randomized to high-dose Qsymia or placebo and treated for 28 weeks. Overnight polysomnograms were obtained at baseline and Week 28. Heart rate was recorded continuously by polysomnography. By Week 28, the mean percent reduction in body weight in the placebo group was 4.2% and 10.3% in the high-dose Qsymia group (p=0.0006).

As measured by polysomnogram, the mean changes in overnight heart rate from baseline to Week 28 were -3.3 bpm and -4.8 bpm in the placebo and high-dose Qsymia groups, respectively. Although the difference between groups was not statistically significant, the effect of high-dose Qsymia on nocturnal heart rate is encouraging.

Cardiovascular Risk

Historically, the development programs for weight management drugs have been composed of largely early middle-aged Caucasian women at low short-term risk for cardiovascular events. This was the case for the Qsymia development program. As a result, there were few major adverse cardiovascular events recorded in the Qsymia program. Nevertheless, in response to the CRL, the applicant adjudicated potential major adverse cardiovascular events from the completed phase 2 and 3 clinical trials. These analyses are defined as follows:

- Cardiovascular Death, MI, and Stroke (applicant adjudicated);

- Major adverse cardiovascular events as used in the rosuvastatin JUPITER trial (applicant adjudicated): Cardiovascular Death, MI, Stroke, Coronary Revascularization, and Unstable Angina;

- FDA MACE (applicant adjudicated): Cardiovascular Death, MI, Stroke, Coronary Revascularization, Unstable Angina, and Congestive Heart Failure;

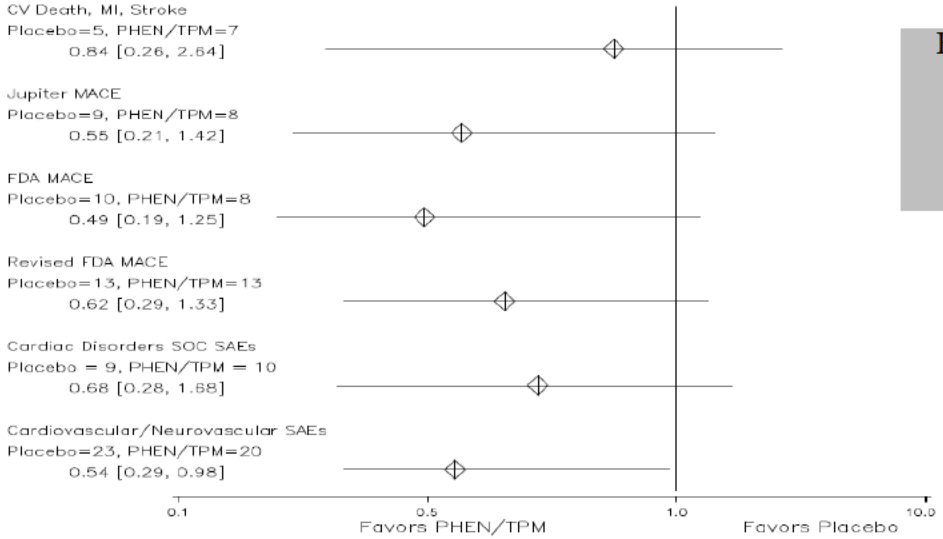
- Revised FDA MACE (applicant adjudicated): Cardiovascular Death, Acute Coronary Syndrome (Non-fatal MI and Unstable Angina), Cerebrovascular Events (Non-fatal Stroke and Transient Ischemic Attack), Coronary Revascularization, Hospitalization for Heart Failure, Stent Thrombosis, Hospitalization for Other Cardiovascular Causes, Carotid Artery Revascularization, Peripheral Vascular Revascularization, Lower Extremity Amputation, Hospitalization for Cardiac Arrhythmia;

- Cardiac Disorders System Organ Class (SOC) serious adverse events (SAEs): All SAE preferred terms mapping to the Medical Dictionary for Regulatory Activities (MedDRA) Cardiac Disorders SOC;

- Cardiovascular and Neurovascular SAEs: All SAE preferred terms mapping to the MedDRA Cardiac Disorders SOC, and SAEs with preferred terms of deep vein thrombosis, hypertension, hypotension, brain stem infarction, cerebral infarction, cerebrovascular accident, hemorrhage intracranial, transient ischemic attack, chest pain, non-cardiac chest pain, and pulmonary embolism

The results of these analyses are shown in the following forest plot excerpted from Dr. Roberts' review.

Incidence of Adverse Cardiovascular Events from Qsymia Clinical Trials



BEST AVAILABLE COPY

CV = cardiovascular; JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; MACE = major adverse cardiovascular events; MI = myocardial infarction; PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate; SAE = serious adverse event; SOC = system organ class.
Source: ISS Post-text Table S39.1

Though based on small numbers of events (hence the wide confidence intervals), it is reassuring that the point estimates of risk for cardiovascular events are all below unity for Qsymia compared with placebo.

8. Advisory Committee Meeting

A second EMDAC meeting for Qsymia was convened on 22 February 2012. The meeting focused on the teratogenicity data for topiramate and the applicant's proposed REMS, as well as data regarding Qsymia's effect on blood pressure and pulse.

When asked if the available data justified requiring that a cardiovascular outcomes trial be conducted prior to approval, the committee, with the exception of one member, did not feel strongly that an outcomes trial needed to be conducted before approval. When asked if the overall benefit-risk assessment supported approval of Qsymia for the treatment of obesity in individuals with a BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 when accompanied by a weight-related comorbidity, 20 committee members voted "yes" and two voted "no." Of note, a number of the "yes" votes were cast by individuals who voted against approval at the first Qsymia EMDAC meeting.

The Division's recent experience with the assessment of cardiovascular safety of drugs to treat diabetes, the publication of the Sibutramine Cardiovascular Outcomes (SCOUT) trial in September 2010, and the subsequent removal of sibutramine from the market provided the impetus to hold an EMDAC meeting on 28 and 29 March 2012 to discuss the cardiovascular safety assessment of weight management drugs. There was general agreement among the committee members that all new obesity drugs should be evaluated for cardiovascular safety in a manner similar to that used for diabetes drugs - i.e., the ruling out of pre- and post-approval degrees of cardiovascular risk. As of this writing, the Agency has not formulated an official policy regarding the March 2012 EMDAC recommendation. Pending this policy decision, I believe the totality of data support the post-approval conduct of a cardiovascular outcomes trial with Qsymia.

9. Pediatrics

The sponsor requested a waiver of pediatric studies in subjects (b) (4) The Division met with the Pediatric Review Committee and concluded that the applicant will be granted a waiver for studies in pediatric patients aged 0 – 6 years and will receive deferrals for studies in pediatric patients aged 7 – 11 years and 12 – (b) (4) years. The applicant will be required to conduct a juvenile animal study before multiple-dose clinical studies of Qsymia are initiated in pediatric patients.

10. Other Relevant Regulatory Issues

Risk Evaluation and Mitigation Strategies (REMS)

Data provided in the applicant's complete response suggest that exposure to Qsymia during the first trimester of pregnancy will increase the risk for oral clefts. To mitigate this risk, the applicant proposed contraindicating the use of Qsymia in WOCBP. Given that drugs with greater teratogenic risk than Qsymia (e.g., isotretinoin) are not contraindicated in WOCBP, it would be difficult to justify applying this restriction to Qsymia. In addition, it would be false to claim that there are no WOCBP for whom the benefits of Qsymia would not outweigh the risk of teratogenicity. A highly-restrictive REMS, moreover, would likely have the unintended consequence of increasing off-label use of the individuals drugs, phentermine (approved for short-term weight loss) and topiramate (approved for seizures and migraine prophylaxis), neither of which have a REMS or any restriction on access. In this scenario, the educational component of the Qsymia REMS would not reach the target population. Lastly, the legislation governing REMS requires that risk mitigation strategies not be unduly burdensome on patient access to the drug. One could argue that a highly-restrictive REMS for Qsymia - e.g., women of child-bearing age must provide evidence that they are not of child-bearing potential and WOCBP must provide evidence that they are not pregnant before receiving each monthly refill - would be unduly burdensome.

Consequently, I agree with colleagues from the Division of Risk Management and with Dr. Egan that to ensure the benefits of Qsymia outweigh the risk for teratogenicity, a REMS, which does not contraindicate the use of the drug in WOCBP, is appropriate and will be required for approval.

The goals of the Qsymia REMS are to inform prescribers and female patients of reproductive potential about: 1) the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy, 2) the importance of pregnancy prevention for females of reproductive potential receiving Qsymia, and 3) the need to discontinue Qsymia immediately if pregnancy occurs.

The key elements of the REMS are: 1) a medication guide, 2) elements to assure safe use, and 3) an implementation system. Components of the elements to assure safe use include the training of healthcare professionals who prescribe Qsymia and the dispensing of Qsymia by specially certified mail-order pharmacies. An implementation system will be established to monitor and evaluate whether the elements to assure safe use are meeting the program's goals.

Post-Marketing Studies

In addition to the studies required under the Pediatric Research and Equity Act, the applicant will be required to conduct six post-marketing studies under section 505(o) of the Food, Drug, and Cosmetic Act. In brief these are 1) a juvenile animal study to assess the effect of the approved drug on behavior, learning and memory, ocular toxicity, and bone/teeth development; 2) an *in-vitro* study to determine the inhibitory potential of the approved drug on renal transporters; 3) a prospective cohort study to determine the frequency of pregnancy in women of child-bearing potential prescribed Qsymia and compare the risk of oral clefts, major congenital malformations, and low birth weight in offspring of women exposed to Qsymia; 4)

a drug use study to characterize the real-world use of Qsymia (e.g., average, median, and range for duration of use); 5) a controlled clinical trial to evaluate the effect of Qsymia on glomerular filtration rate; and 6) a controlled clinical trial to evaluate the effect of Qsymia on the incidence of major adverse cardiovascular events.

Financial Disclosure

Dr. Roberts notes in her review that one investigator received significant payments defined as monetary value of greater than $25,000 from the applicant. This investigator's study site was audited by the Office of Scientific Investigations. (b) (6) the data generated by this investigator were deemed acceptable.

Inspections

Routine inspections by the Office of Scientific Investigations did not uncover any significant deficiencies or irregularities in reporting of clinical data.

Tradename Evaluation

The Division of Medication Error and Prevention Analysis and the Office of Prescription Drug Promotion concluded that the proposed tradename, Qsymia, is acceptable from safety and promotional standpoints, respectively. I agree with these assessments.

11. Labeling

Some key features of the approved labeling include:

- The indication will be for chronic weight management (b) (4) including weight loss and maintenance of lost weight, which is the indication language that was used for orlistat, the only weight-loss drug approved for long-term use. The newly-worded indication aligns with the recommendation made in the Agency's 2007 draft guidance for weight management drugs.

- Limitations of use statements will highlight 1) that the safety of Qsymia when used with other products intended for weight loss – prescription drugs, nonprescription drugs, and herbal or dietary supplement – has not been determined, and 2) that the effect of Qsymia on cardiovascular morbidity and mortality has not been determined.

- In an effort to limit unnecessary exposure to Qsymia and maximize benefits over risks, the labeling will state that patients taking mid-dose Qsymia who do not lose at least 3% of baseline body weight by 12 weeks of treatment should discontinue the drug or increase the dose, as it is unlikely that they will achieve and sustain clinically meaningful weight loss.

- If a patient has not lost at least 5% of baseline body weight on high-dose Qsymia after 12 weeks of treatment, the labeling will recommend that the drug be discontinued, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

- Qsymia will be contraindicated during pregnancy and will be a category X drug.

- Regular measurement of resting heart rate will be recommended for all patients taking Qsymia, especially in patients with (b) (4) cardiac or cerebrovascular disease or when initiating or increasing the dose of Qsymia.

- The labeling will also note that Qsymia has not been studied in patients with recent or unstable cardiac or cerebrovascular disease and therefore use is not recommended in such patients.

- For patients who experience a sustained increase in resting heart rate while taking Qsymia, the labeling will indicate that the dose should be reduced or Qsymia discontinued.

12. Decision/Action/Risk Benefit Assessment

I agree with Dr. Roberts that Qsymia should be approved.

All three doses of Qsymia satisfied one or both of the Agency's efficacy criteria for a weight management drug. The mid and high doses produced the largest amounts of placebo-subtracted weight loss of any weight management drug that the Division has reviewed for regulatory approval. With the exception of heart rate, relative to placebo, treatment with Qsymia was associated with favorable changes in common weight-related comorbidities. Over the course of one year, patients treated with the mid and high doses of Qsymia had a reduced incidence of developing type 2 diabetes. Use of Qsymia was associated with the initiation of fewer anti-diabetic and anti-hypertensive medications.

Qsymia was not approved during the first review cycle because of concerns about teratogenicity, specifically, oral clefts, and the lack of an adequate REMS to address this concern.

Data provided in the applicant's complete response suggest that exposure to Qsymia during the first trimester of pregnancy will increase the risk for oral clefts. To mitigate this risk, Qsymia will require a REMS that provides physician education and limits distribution of the drug to certified pharmacies. The REMS will help ensure that WOCBP receive the information needed to reduce the risk of teratogenic harm from Qsymia without being unduly burdensome on patient access to the drug or so restrictive that it encourages prescribers and patients to circumvent the REMS by using the individual component drugs together in an off-label manner.

Qsymia is associated with a small mean increase in heart rate; however, the drug reduces blood pressure such that the change in the RPP – a surrogate of myocardial oxygen demand - is

similar for Qsymia and placebo-treated subjects. In addition, analyses of cardiovascular-related adverse event data from the Qsymia phase 2 and 3 clinical trials, while limited in scope, do not raise concern of excessive risk.

One advisory committee member at the February 2012 EMDAC meeting voiced serious concern about Qsymia's effect on heart rate and risk for cardiovascular disease. However, I agree with other committee members who did not believe that this "risk" outweighs the benefits of the drug, or that it justifies conduct of a cardiovascular outcomes trial prior to approval. Because individuals at high risk for cardiovascular events, such as those who have had a recent myocardial infarction or stroke, were not included in the Qsymia clinical trials, the labeling will recommend against use of the drug in this patient population.

To summarize, within the framework of the approved REMS and labeling, I believe the currently-available data support approval of Qsymia for chronic weight management in patients with a BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 when accompanied by a weight-related comorbidity.

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

/s/

ERIC C COLMAN
07/17/2012