

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: July 17, 2012

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Drug Name(s): QSYMIA (phentermine and topiramate extended-release)

Therapeutic Class: Combination comprising an anti-epileptic and a
sympathomimetic amine anorectic

Dosage and Route: 3.75 mg phentermine/23 mg topiramate orally daily for 14
days, then 7.5 mg phentermine/46 mg topiramate orally
daily

Application Type/Number: 022580

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Applicant/sponsor: Vivus, Inc

OSE RCM #: 2011-4184

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1 INTRODUCTION

1.1 BACKGROUND

Qsymia is a combination product containing immediate-release phentermine hydrochloride (PHEN) and extended-release topiramate (TPM). Qsymia, has four dosage strengths, 3.75 mg PHEN/23 mg TPM, 7.5 mg PHEN/46 mg TPM, 11.25 mg PHEN/69 mg TPM, and 15 mg PHEN/92 mg TPM. The recommended maintenance dose is 7.5 mg PHEN/46 mg TPM once daily. The proposed indication is for the treatment of obesity, including weight loss and maintenance of weight loss to be used in conjunction with diet and exercise in obese patients ($\text{BMI} \geq 30 \text{ kg/m}^2$) or overweight patients ($\text{BMI} \geq 27 \text{ kg/m}^2$) with weight-related co-morbidities.

The individual components of Qsymia, topiramate and phentermine, have been available in the United States since 1996 and 1959, respectively. Topiramate was first approved by the FDA in 1996 for the treatment of epilepsy, and subsequently received approval in 2004 for prophylaxis of migraine headaches. Phentermine has been approved in the US since 1959, and is indicated as a short-term adjunct as part of a regimen of weight reduction.

Topiramate has been shown to increase the risk of oral clefts. Data from the North American AED and Pregnancy Registry (NAAPR) showed a 10 times higher than the expected incidence in women treated with topiramate during pregnancy.¹ Data from the Slone Epidemiology Center Birth Defects Study (BDS) and the Center for Disease Control's National Birth Defects Prevention Study (NBDPS) suggest that first trimester topiramate exposure may confer an increased risk of oral clefts with a combined odds ratio of 5.2 (95% CI 1.4-19.5)².

If the application for Qsymia is approved by the FDA, Qsymia would likely be used largely by females, especially females of reproductive potential. In 2009, the last full year that the weight loss drug, Meridia (sibutramine), was marketed, the patients using Meridia were 83% female, and 67% were 21 to 50 years of age. In 2001, the year that Meridia was most prescribed, over (b) (4) prescriptions were written for Meridia.³ The total weight loss prescription market, including the combined prescribing of fenfluramine and phentermine exceeded (b) (4) prescriptions in 1996, the year of most prescribing of weight loss drugs.⁴ These data suggest that Qsymia would likely be used by many females of reproductive potential, especially if Qsymia is perceived by prescribers and patients as being effective in helping patients achieve weight loss.

¹ Holmes LB et al. Annual Report on 7,189 exposed pregnancies from the North American AED Pregnancy Registry. April 15, 2011

² Margulis AV et al. Use of Topiramate in Pregnancy and the Risk of Oral Clefts. Pharmcoepidemiology and Drug Safety 2011;20: S11. Abstract presented at the 27th ICPE 2011 meeting.

³ Border-Hemphill V. Meridia use data presented at September 2010 CDER Center Director Briefing.

⁴ Roberts M. Total number of prescription weight loss drugs dispensed 1990-2003 in retail pharmacies. Data presented at December 2011 meeting of CDER REMS Oversight Committee.

Fetal toxicity is included in the Topamax labeling in the *Warnings and Precautions*, *Use In Specific Populations*, and *Patient Counseling Information* sections of the labeling. Phentermine is contraindicated for use during pregnancy. A REMS comprising a Medication Guide and a timetable for submission of assessments was required for topiramate to mitigate the risk of suicidality. This requirement was removed in June 2011, and no REMS is required currently for topiramate. A REMS has never been required for the marketing of phentermine.

1.2 REGULATORY HISTORY

On December 28, 2009, Vivus submitted a new drug application (NDA 022580) for Qsymia (previous proposed tradename was Qnexa) to support the following proposed indication:

For the treatment of obesity, including weight loss and maintenance of weight loss and should be used in conjunction with diet and exercise. QNEXA is recommended for:

- *Obese patients (BMI ≥ 30 kg/m²), or*
- *Overweight patients (BMI ≥ 27 kg/m²) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity)*

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.

DMEP issued a Complete Response (CR) letter on October 28, 2010, citing as deficiencies the incomplete characterization of the potential adverse cardiovascular effects (i.e., increased heart rate) and an insufficient assessment of Qsymia’s teratogenic potential.

In response to the CR letter, Vivus submitted additional information to support approval of the NDA; the resubmission included a REMS submission.

The sponsor’s original REMS proposal for Qsymia included a (b) (4) certification of prescribers, dispensing by certified pharmacies, and a safe-use condition of dispensing only to male patients and female patients not of reproductive potential. The sponsor’s proposal and elements needed for a REMS for Qsymia were discussed internally within the FDA and externally at the February 22, 2012 meeting of the Endocrine and Metabolic Drugs Advisory Committee. The committee supported approval of the application with a REMS.

The following are regulatory milestones pertinent to the REMS for Qsymia during the second review cycle:

- February 22, 2012—the resubmitted application was considered by the Endocrine and Metabolic Drugs Advisory Committee; the committee voted 20-2 recommending approval of the application. Many committee members cited the REMS in their decision to support approval of the application. Of the committee members who supported approval with a REMS, most supported the REMS presented; that is, a REMS utilizing prescriber training not linked to prescribing rights and certified pharmacies. Two members thought that mandatory prescriber training should be included in the REMS. Two members did not support use of mail order pharmacies in the REMS, citing a loss of face-to-face interaction with pharmacists, the potential for late medication deliveries, and the lack of universal patient coverage with mail order pharmacies.
- March 21, 2012—the FDA and the applicant met to discuss the REMS; REMS interim comments set #1 was prepared by the FDA for this face-to-face meeting.
- April 4, 2012—applicant submitted a REMS proposal based on the REMS outlined at the February 22, 2012 advisory committee meeting and the March 21, 2012 face-to-face meeting.
- April 6, 2012—FDA notified the applicant that the April 4, 2012 submission constituted a major amendment; the user fee goal date was extended to July 17, 2012.
- May 16, 2012—interim FDA REMS comments were sent to the sponsor.
- June 4, 2012—the applicant sent a revised REMS document that proposed to change the certification requirements for pharmacies to be permitted to dispense Qsymia within the REMS. The change would have deleted the requirement for the certified pharmacies to submit identities of prescribers to the applicant to allow the applicant to train previously untrained prescribers on the REMS. Subsequently, in a teleconference with the FDA, the applicant agreed to submit a written justification for the change.
- July 12, 2012—the sponsor met with the Agency to resolve issues surrounding the REMS
- July 14, 2012—the sponsor emailed the REMS, REMS Supporting Document and REMS materials incorporating changes agreed upon at the July 12, 2012 meeting
- July 17, 2012—the applicant submitted a revised REMS proposal

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

We reviewed the following:

- The proposed REMS submitted July 17, 2012.
- Qnexa REMS Options Review, Yancey C.L. signed in DARRTS on October 2010.
- Clinical Briefing Document prepared for the February 22, 2012 meeting of the Endocrine and Metabolic Drugs Advisory Committee, Roberts M.

2.2 ANALYSIS TECHNIQUES

The REMS and REMS materials were reviewed for conformity with previous FDA comments and for alignment with the REMS provisions in the Food and Drug Administration Amendments Act (FDAAA).

The Food and Drug Administration Amendments Act (FDAAA) of 2007 requires that the Agency consider six factors in determining whether a REMS is needed for a given product. These factors are: the estimated size of the population likely to use the drug involved, the seriousness of the disease or condition that is to be treated with the drug, the expected benefit of the drug with respect to such disease or condition, the expected or actual duration of treatment with the drug, the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug, and whether the drug is a new molecular entity. After considering these factors, a REMS should be instituted for a product if the REMS is needed to ensure that the benefits of the product outweigh its risks.

The data for the six factors for Qsymia are detailed below.

- The estimated size of the population likely to use the drug involved.
 - Most adults in the United States are either obese or overweight. At its maximum in 2001, (b)(4) prescriptions were written for sibutramine⁵. The population who might use Qsymia could meet or exceed (b)(4) prescriptions annually.
- The seriousness of the disease or condition that is to be treated with the drug.

⁵ Simone P. Pinheiro, Vicky Borders-Hemphill. CDER/OSE/DEPI January 11, 2010 review. Cardiovascular adverse outcomes with use of sibutramine.

- Overweight and obesity are serious, chronic conditions that increase the risk of coronary artery disease, hypertension, Type 2 diabetes, gallstones, respiratory illness, and some cancers⁶.
- The expected benefit of the drug with respect to such disease or condition.
 - Although no head-to-head clinical trials have been conducted between Qsymia and other weight loss drugs, the data suggest that Qsymia therapy achieves greater weight loss than other weight loss pharmacotherapies. Treatment with Qsymia resulted in a mean weight loss of 11.4 kg at one year. Other weight loss drugs (Orlistat, sibutramine, lorcaserin, Contrave) achieved mean weight loss at one year from 5.8 kg to 6.4 kg⁷.
- The expected or actual duration of treatment with the drug.
 - Patients are treated with Qsymia chronically unless they have not lost 3% of body weight by week 12 (the dose can either be escalated or the drug stopped for patients who have not lost 3% of body weight by week 12) and 5% of body weight by week 24. Of the patients enrolled in the 1-year clinical trials, 63% continued treatment for the entire year. Select patients continued another year of treatment with Qsymia. Of these, 66% completed the second year of treatment.
- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
 - The most concerning safety issue with Qsymia is teratogenicity, specifically the risk of oral clefts.
- Whether the drug is a new molecular entity (NME).
 - Qsymia is not an NME.

3 RESULTS OF REVIEW OF PROPOSED QSYMIA RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM OR POSTMARKETING EXPOSURE

Qsymia was studied in two one-year trials of approximately 3,700 overweight or obese adults. Treatment with Qsymia resulted in a statistically significant placebo-subtracted mean percent weight loss of 6.7% for patients receiving mid-dose Qsymia and 8.9% for patients receiving high-dose Qsymia. With respect to the FDA's categorical efficacy standard of weight loss, 62% and 70% of overweight and obese adults treated with mid- and high-dose Qsymia, respectively, lost $\geq 5\%$ of their body weight compared to 20% treated with placebo. The results of these two trials meet the FDA standards establishing efficacy of a weight loss drug.

⁶ National Institutes of Health, url <http://www.nhlbi.nih.gov/health/health-topics/topics/obe/>. Accessed July 3, 2012.

⁷ Mary Roberts. Background document prepared for December 2, 2011 meeting of FDA's REMS Oversight Committee.

3.2 SAFETY CONCERNS

During the original NDA review, the medical review focused on psychiatric, cognitive, metabolic, and cardiovascular adverse events. DMEP and DRISK determined that these adverse events could be handled with routine measures (labeling and pharmacovigilance), and the events did not require a REMS.

The most concerning safety issue with Qsymia is teratogenicity, especially because, if Qsymia is used in a similar patient population compared to past weight loss drugs, most of the potentially large market for Qsymia will be females of reproductive potential. Qsymia will likely be used by hundreds of thousands to millions of females of reproductive potential.

Topiramate has been shown to increase the risk of oral clefts. In the 2011 annual report of the North American AED and Pregnancy Registry (NAAPR), there were 4 oral clefts among 347 pregnancies exposed to topiramate. This is about 10 times higher than the expected incidence.⁸

A sponsor-funded study from the Wolters Kluwer Pharma Solutions Source Lx Patient Longitudinal database, which tracks patients' pharmacy and medical claims, showed rates of oral clefts of 0.23% following first trimester topiramate exposure. The prevalence rate in this database was close to the expected background prevalence of about 0.12 to 0.15%.

Data from the Slone Epidemiology Center Birth Defects Study (BDS) and the Center for Disease Control's National Birth Defects Prevention Study (NBDPS) suggest that first trimester topiramate exposure may confer an increased risk of oral clefts with a combined odds ratio of 5.2 (95% CI 1.4-19.5)⁹.

There were 34 pregnancies in the Qsymia clinical development program. The pregnancies were discovered at an average gestational age of 5.4 weeks. No major malformations were found in 19 newborns from the 34 pregnancies.

In March 2011, the pregnancy category for Topomax was changed pregnancy category D because of the evidence supporting a conclusion that topiramate can increase the risk of oral clefts.

3.3 GOALS

The goals of the REMS are—

To inform prescribers and female patients of reproductive potential about:

- the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qnexa during the first trimester of pregnancy
- the importance of pregnancy prevention for females of reproductive potential receiving Qnexa
- the need to discontinue Qnexa immediately if pregnancy occurs

⁸ Holmes LB et al. Annual Report on 7,189 exposed pregnancies from the North American AED Pregnancy Registry. April 15, 2011

⁹ Margulis AV et al. Use of Topiramate in Pregnancy and the Risk of Oral Clefts. *Pharmcoepidemiology and Drug Safety* 2011;20: S11. Abstract presented at the 27th ICPE 2011 meeting.

3.4 REMS ELEMENTS

The sponsor originally proposed to [REDACTED] (b) (4)

The sponsor's original REMS proposal to [REDACTED] (b) (4)
[REDACTED] was considered but rejected by the Agency. The Agency
considered the [REDACTED] (b) (4)

3.4.1 Medication Guide

The REMS includes the Qsymia Medication Guide. A Medication Guide will be dispensed to the patient with each prescription.

3.4.2 Communication Plan

The REMS does not include a communication plan.

3.4.3 Elements to Assure Safe Use

3.4.3.1 Training will be provided to healthcare providers who prescribe Qsymia

The following are components of the healthcare provider training.

- a. Vivus will ensure that training is made available to healthcare providers who prescribe Qsymia. Training will be accomplished via online training available at the Qsymia REMS website, electronic training or print training modules available from Vivus medical liaisons during prescriber visits, at professional society meetings, and at medical educational venues.
- b. Vivus will maintain a database of all prescribers who have completed the training. Completion of the training will be defined as
 - i. For electronic training completed independently by the HCP, viewing of all module training screens and completion of post-training knowledge assessment questions,
 - ii. For training modules delivered in person by VIVUS medical liaison, a statement from the medical liaison that all training materials were reviewed and the post-training knowledge assessment questions were completed
 - iii. For print training modules completed independently by the HCP, mailing or faxing a tear-off statement to VIVUS acknowledging full review of materials and completion of the post-training knowledge assessment questions.

- c. On a monthly basis, Vivus will compare this database of trained prescribers with the list of prescribers maintained by certified pharmacies to identify those Qsymia prescribers who have not yet completed the training, and will contact the identified prescribers to complete training. Ninety five percent of untrained prescribers will be contacted and provided training materials or access to such materials within 30 days of identification.
- d. Vivus will inform HCP's who have prescribed Qsymia of any substantial changes to the Qsymia REMS program, including significant changes to the operation of the program, or changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of Qsymia.
- e. Vivus will ensure that, as part of training, the following materials are available to prescribers and medical practices:
- i. patient brochure, *Risk of Birth Defects with Qsymia*
 - ii. *Healthcare Provider Counseling Tool for Females of Reproductive Potential*
 - iii. *Prescriber Dosing and Management Checklist*
- f. A Dear Healthcare Provider (DHCP) letter will be sent within 60 days of product approval and again at 12 and 24 months after product approval. The initial DHCP letter will be sent to healthcare providers who are likely to prescribe Qsymia or have written a prescription for an obesity medical treatment within the prior 12 month period. This includes, but is not limited to, general practitioners, family practitioners, internists, gynecologists, endocrinologists, cardiologists, and nurse practitioners/physician assistants. Subsequent DHCP letters will be sent to healthcare providers who are likely to prescribe Qsymia (as described above), healthcare providers who have written a prescription for an obesity medical treatment in the prior 12 months, and any healthcare provider who has prescribed Qsymia within the prior 12 month period. Vivus will distribute the DHCP letters via electronic mail, through the mail, or via facsimile. The DHCP letter will include a link to the Qsymia REMS website landing page.

At the same interval, Vivus will send a Dear Medical Society letter to the professional organizations of likely prescribers, and will request that the letter be provided to their members

Vivus will make the REMS, the training materials, the DHCP and Dear Medical Society letters, the patient brochure entitled *Risk of Birth Defects with Qsymia*, the *Healthcare Provider Counseling Tool for Females of Reproductive Potential*, the *Prescriber Dosing and Management Checklist*, and professional labeling (including the Medication Guide) available via a dedicated REMS-specific link from the Qsymia website as well as through Vivus' medical information department.

- g. Vivus will maintain a Program Coordinating Center with a Call Center to support prescribers and patients in interfacing with the REMS. Vivus will ensure

that all materials listed in or appended to the Qsymia REMS will be available through the REMS Program website or by calling the Call Center.

Comment:

Prescriber training will not be linked to drug distribution but Vivus will ensure that the materials are available to all healthcare providers likely to prescribe Qsymia and will take steps to identify prescribers to complete training.

3.4.3.2 Vivus will contract with and certify pharmacies to dispense Qsymia. To become certified, the pharmacy must agree:

- a. To provide a Medication Guide and patient brochure entitled *Risk of Birth Defects with Qsymia* each time Qsymia is dispensed.
- b. To refrain from reselling or transferring Qsymia to another pharmacy or distributor.
- c. To train all pharmacists and staff involved with the dispensing of Qsymia to provide a Medication Guide and a patient brochure entitled *Risk of Birth Defects with Qsymia* each time Qsymia is dispensed.
- d. To maintain a list of Qsymia prescribers that will be made available to Vivus upon request.

Vivus will maintain a link to the list of certified pharmacies on the REMS website.

Comment:

Dispensing through certified pharmacies was proposed by the sponsor and presented to the advisory committee. The sponsor argued, and the Agency agreed, that dispensing through certified pharmacies would ensure that the Medication Guide and the patient brochure, *Risk of Birth Defects with Qsymia*, are provided to patients with each prescription and each refill. Dispensing through certified pharmacies would also facilitate identification and training of prescribers and providing educational materials to prescribers.

The sponsor originally proposed to certify only mail order pharmacies because they were the only pharmacies thought to be capable of complying with the certification requirements. Late in the review cycle, on June 4, 2012, the applicant sent a revised REMS document that proposed to change the certification requirements for pharmacies and to permit retail pharmacies to become certified. Details regarding the new dispensing plan were provided to the Agency for review less than two weeks prior to the PDUFA date. As the review team began to review the changes, it became apparent that many details supporting the new dispensing plan had not been resolved, and it would not be possible to resolve all issues by the PDUFA date. Therefore, the Agency asked the sponsor to reinstate the original dispensing plan, and to submit the new dispensing plan as a REMS modification after action on the pending application. At a July 12, 2012 meeting, the sponsor agreed to reinstate the original dispensing plan, and all remaining REMS issues with the dispensing plan were resolved.

3.4.4 Implementation System

The REMS implementation system includes the following.

- a. Vivus will ensure that pharmacies dispensing Qsymia are specially certified using the criteria described above.
- b. Vivus will ensure that Qsymia is distributed only to pharmacies certified in the Qsymia REMS program.
- c. Vivus will monitor distribution data and prescription data to ensure that only certified pharmacies are dispensing Qsymia.
- d. Vivus will monitor and audit the dispensing systems to check that all processes and procedures are in place and functioning to support the requirements of the Qsymia REMS; that is, to ensure that the Medication Guide and patient brochure entitled *Risk of Birth Defects with Qsymia* are being dispensed with each prescription, that Qsymia is not being resold or transferred to another pharmacy or distributor, that all pharmacists and other staff involved with dispensing are trained, and that a list of prescribers is maintained and made available to Vivus upon request.
- e. Vivus will receive regular reports and conduct audits of certified pharmacies to ensure that Qsymia is being dispensed according to the specified REMS requirements. All pharmacies will be audited in year one and every two years thereafter. If a certified pharmacy is found to be non-compliant, Vivus will institute corrective action
- f. If there are substantive changes to the Qsymia REMS or REMS program, Vivus will update all affected materials and notify certified pharmacies. Substantive changes are defined as:
 - i. Significant changes to the operation of the Qsymia REMS or REMS Program, or
 - ii. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of Qsymia
- g. Based on monitoring and evaluation of these elements to assure safe use, Vivus will take reasonable steps to improve implementation of these elements to meet the goals of the REMS.

3.4.5 Timetable for Submission of Assessments

Vivus will submit REMS Assessments to FDA at 6 months and 12 months from the date of initial approval of this REMS, and annually thereafter.

3.5 REMS ASSESSMENT PLAN

The REMS assessment plan should include, but is not limited to, the following:

The REMS assessment reports submitted at 12 months from the date of initial approval of the REMS and annually thereafter will include—

1. Results of an evaluation of patients' understanding of the serious risks of Qsymia (phentermine and topiramate extended-release)

2. Using data obtained from surveys of patients and prescribers, an evaluation of the extent that females of reproductive potential were counseled about pregnancy prevention and contraceptive use
3. Using data obtained from surveys of patients, an evaluation of contraceptive use by females of reproductive potential
4. An assessment of healthcare providers' awareness of:
 - a. The serious risks of Qsymia (phentermine and topiramate extended-release)
 - b. The need to exclude a pregnancy before initiating Qsymia therapy
 - c. The need for patients to consistently use effective birth control and what the effective methods of contraception are
 - d. The need to promptly discontinue Qsymia therapy in the event of a pregnancy
5. A report on pharmacy failures to adhere to distribution and dispensing requirements based on audits conducted by Vivus.

The REMS assessment reports submitted at 6 months and 12 months from the date of initial approval of the REMS and annually thereafter will include—

6. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24 and patient brochure, entitled *The Risk of Birth Defects with Qsymia*.
7. With regard to the Dear Healthcare Provider (DHCP) letter sent during the reporting period:
 - a. The date of initial mailing of the DHCP letter to healthcare providers and professional organizations, and the dates of subsequent mailings
 - b. The number of recipients of the DHCP letter
 - c. A copy of all documents included in each distribution of the DHCP letter
 - d. Data establishing the date, number and specialty of healthcare providers (HCPs) targeted with the DHCP letter via email; the number and specialty of HCPs who received the email; the number and specialty of HCPs who opened the email; the number of emails that were undeliverable; the number of letters sent via hard copy and the number distributed by sales representatives; the names of professional organizations contacted to distribute the DHCP letter to their members; the names of the organizations that accepted and redistributed the letter; and the names of the professional organizations that declined to accept or redistribute the DHCP letter
8. An assessment of the percentage of not-yet-trained prescribers who are presented with REMS materials via Sales Specialists, medical liaisons, or medical information department during the reporting period
9. An assessment of the number and percentage of unique prescribers who complete the educational training (during the reporting period and cumulative) as defined within the REMS
 - a. For electronic training, viewing of all module training screens or pages and completion of post-training assessment questions

- b. For print training modules delivered in person by medical liaison, a statement by the medical liaison that the training module was completed
 - c. For print training modules completed independently by the HCP, mailing or faxing a tear-off statement of completion of the training
10. An assessment of strategies that have been employed during the reporting period to encourage prescribers to undergo educational training
 11. The number and names of certified pharmacies under agreement with Vivus for this program, including newly certified pharmacies
 12. A report on any dispensing of Qsymia that occurs outside of certified pharmacies, including the number of instances and the amount dispensed, and corrective actions taken to address the dispensing of Qsymia outside the REMS
 13. The number and names of pharmacies decertified and the reason for the decertification
 14. A report on any distribution of Qsymia that occurs to non-certified pharmacies, including the number of instances, the amount distributed, and corrective action taken to address the distribution of Qsymia to non-certified pharmacies
 15. Data from the reporting period on patients receiving Qsymia including dosage strength prescribed, , duration of use, episodes of use per patient, length of break in use for patients with multiple episodes of use
 16. Data on prescribers of Qsymia including the number of unique prescribers prescribing Qsymia, (during the reporting period and cumulative)
 17. A summary of REMS Call Center activity including frequently asked questions and frequently reported problems
 18. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

3.6 PROPOSED POSTMARKETING STUDIES

Two post-marketing studies are proposed that could be important to assessing the teratogenicity risk and the impact of the REMS:

1. A prospective cohort study to a) determine the frequency of pregnancy in women of child-bearing age prescribed Qsymia and b) compare the risk of oral clefts, major congenital malformations, and low birth weight in offspring of women exposed to Qsymia during pregnancy with offspring of similar women not exposed to Qsymia during pregnancy.
2. A drug use study conducted annually for 7 years with nationally representative and projected data to provide the following about patients prescribed Qsymia: a) the estimated total number of prescriptions and patients dispensed Qsymia per year; b) distribution of patients by age, sex, and BMI; c) distribution of prescribers by specialty; d) average, median, and range for duration of use; e) average and median size of prescriptions; f) prescribed average daily dose; g) frequencies of top 10 concomitant diagnoses (including pregnancy) by age and sex; h) frequencies of top 10 concomitant drugs by age and sex (including contraceptive medications for females of childbearing age).

4 DISCUSSION

There is need for an effective weight loss treatment. To establish efficacy, the Agency requires that a weight loss drug show at least 5% higher average weight loss compared to placebo, or it must cause at least 35% of treated people to lose at least 5% of their initial body weight, the proportion who lose 5% of body weight should be about double that observed in the placebo group, and the difference should be statistically significant. Qsymia met both the Agency's efficacy requirements for mean weight loss and for the proportion of patients who lose at least 5% of body weight. Treatment with Qsymia resulted in a statistically significant placebo-subtracted mean percent weight loss of 6.7% for patients receiving mid-dose Qsymia and 8.9% for patients receiving high-dose Qsymia. With respect to the FDA's categorical efficacy standard of weight loss, 62% and 70% of overweight and obese adults treated with mid- and high-dose Qsymia, respectively, lost $\geq 5\%$ of their body weight compared to 20% treated with placebo. The absolute weight loss with high-dose Qsymia was larger than the weight loss observed in trials submitted for Orlistat, sibutramine, lorcaserin, and naltrexone/bupropion.¹⁰

The efficacy of the combination of topiramate and phentermine in weight loss is becoming known to the medical community and to patients.¹¹ With the expanding awareness of the effectiveness of treatment for weight loss with topiramate and phentermine, the off-label use of the combination of the individual ingredients is likely to expand in the absence of an approved combination product. Arguably, use of the separate ingredients for weight loss without a REMS in place would place patients at greater risk than using Qsymia within a REMS.

The availability of both phentermine and topiramate, without REMS requirements or restrictions, complicates the selection of elements for a REMS for Qsymia. Because the ingredients that comprise Qsymia are available without restriction for other indications, significant barriers to using Qsymia, including restricted distribution with mandatory pregnancy testing for Qsymia alone, would have limited impact. It is likely that some prescribers would prescribe the individual ingredients in an amount that would approximate Qsymia capsules to circumvent the requirements of a restrictive REMS.

The only way to prevent a restrictive REMS for Qsymia from being circumvented, is to require restriction of topiramate for all indications. FDAAA requires that the REMS not be unduly burdensome on patient access to the drug, considering in particular patients with serious or life-threatening diseases or conditions. Over 2 million patients receiving topiramate, most of whom are receiving topiramate for seizures or migraine prophylaxis, would be affected by restrictions placed on topiramate use¹². To successfully implement this and to avoid potential circumventing of this safe-use condition, it would be necessary

¹⁰ Qsymia has not been tested against other weight loss drugs.

¹¹ In an April 18, 2012 episode of *Dr. Oz Show*, the use of topiramate and phentermine for weight loss was described. In its February 16, 2012 issue, the New York Times discussed the use of combination topiramate and phentermine for weight loss.

¹² Vicky Borders-Hemphill, Pharm.D., January 12, 2012. Review of Phentermine and Topiramate use in women of child-bearing potential. FDA/CDER/OSE Division of Epidemiology II (DEPI II).

to put the same restrictions on the distribution of Qsymia, Topamax, and topiramate. It would be extremely burdensome to the health care system and patients to require a REMS for Qsymia, Topomax, and topiramate with mandatory pregnancy testing for females of reproductive potential. Doing so would require that the monthly supply of drug for females of reproductive potential be held until pregnancy testing is conducted and results confirmed. A REMS required for Qsymia should not place undue burden on patients receiving topiramate for seizure disorders and prophylaxis of migraine headaches. At this time, a REMS is not required to assure that the benefits of topiramate exceed its risks for these indications, and any REMS established for Qsymia should not place undue barriers to access for these patients receiving topiramate for other indications.

There were multiple discussions between DMEP, DRISK and senior level CDER management regarding the elements of the REMS and the difficulty of constructing a REMS with the authority granted by FDAAA that would have sufficient outreach and controls to mitigate the risk of teratogenicity of Qsymia without causing access issues for patients who use topiramate for other indications. Agency participants in this discussion struggled with the selection of appropriate REMS elements, and we did not find a perfect solution to this problem. We considered the teratogenic effect of Qsymia, oral clefts. The risk of teratogenicity with Qsymia is concerning, surgery is frequently used to improve functional outcome and aesthetic results, albeit with significant burden to the affected children and their families.

Dispensing through certified pharmacies was proposed by the sponsor. The sponsor argued, and the Agency agreed, that dispensing through certified pharmacies would ensure that the Medication Guide and the patient brochure, *Risk of Birth Defects with Qsymia*, are provided to patients with each prescription and each refill. Dispensing through certified pharmacies would also facilitate identification and training of prescribers and providing educational materials to prescribers.

Based on these considerations, a REMS with prescriber training, not linked to prescribing rights, and dispensing through certified pharmacies were selected as elements to assure safe use in the REMS for Qsymia. The selection of elements balances the need for access and the need to mitigate the risk.

5 CONCLUSION

In conclusion, the amended REMS for Qsymia (phentermine/topiramate capsules, 3.75mg/23mg, 7.5mg/46mg, 11.25mg/69mg, 15mg/92mg), submission of July 17, 2012 submission contains the appropriate and agreed upon revisions on the REMS components. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of the Qsymia REMS in achieving the goals.

Therefore, the Qsymia REMS is acceptable to Division of Risk Management.

6 RECOMMENDATIONS

The OSE, DRISK recommends approval of the Qsymia REMS of July 17, 2012.

We supplied text previously to be included in the approval letter about the information to be included in the REMS assessment reports.

ATTACHMENTS

REMS, REMS Materials, REMS Supporting Document

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/s/

JOYCE P WEAVER
07/17/2012

CLAUDIA B MANZO
07/17/2012
concur

SAFETY REVIEW MEMO

FROM: Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
(DMEP)

TO: Eric Colman, M.D.
Deputy Director
DMEP

DATE: July 16, 2012

SUBJECT: Recommendation on REMS for Qsymia (phentermine and
topiramate extended-release)

NDA #: NDA 022580

BACKGROUND

Qsymia is a fixed-dose combination of two FDA approved drugs, phentermine and topiramate, in an extended-release formulation. Phentermine is a sympathomimetic that was approved in 1959 as short-term therapy for the treatment of obesity. It is available in 15, 30, and 37.5 mg dosage strengths. Topiramate is a carbonic anhydrase inhibitor that was approved in 1996 for the treatment of seizures and in 2004 for migraine prophylaxis. It is available in tablet form in 25, 50, 100 and 200 mg dosage strengths, and in capsule form in 15 and 25 mg dosage strengths. The effect of phentermine on weight loss is likely mediated by release of catecholamines in the hypothalamus, resulting in reduced appetite and decreased food consumption; however, the exact mechanism of action is not known. The effect of topiramate on weight loss is not known, but may be due to its effects on both appetite suppression and satiety enhancement. Three dosage strengths of Qsymia were studied in the clinical development program: 3.75/23 mg (low dose for titration purposes only), 7.5/46 mg (mid dose; recommended dose), and 15/92 mg (high dose).

Qsymia's weight loss efficacy is statistically significant and clinically meaningful. In two Phase 3 trials, placebo-subtracted weight loss at one year was 6.6% for the mid dose and 8.6-9.4% for the high dose. Approximately 62% of patients treated with the mid dose, and 67-70% treated with the high dose, lost at least 5% of their baseline body weight compared with about 20% of patients treated with placebo. With the exception of heart rate, relative to placebo, treatment with Qsymia was associated with improvement in blood pressure, triglyceride levels, HDL-C, LDL-C, and HbA1c. Notably, the incidence of newly-diagnosed type 2 diabetes during the one-year treatment period was reduced by 31% in the mid dose Qsymia group and by 58% in the high dose Qsymia group.

The Agency issued a Complete Response letter after the initial review cycle due to safety concerns, including the teratogenic risk of topiramate and an observed increase in heart rate associated with Qsymia in the Phase 3 clinical trials. To resolve the deficiencies, the sponsor was asked to submit:

- A comprehensive assessment of topiramate's and phentermine/topiramate's teratogenic potential, to include nonclinical and clinical data.
- A detailed plan and strategy to evaluate and mitigate the potential risk for teratogenicity or fetal harm in women of child-bearing potential taking phentermine/topiramate for the treatment of obesity.
- Evidence that the elevations in heart rate associated with phentermine/topiramate do not increase the risk for major adverse cardiovascular events.
- The final study report for Study OB-305, a Phase 3, 1-year extension study of a subgroup of subjects from Study OB-303.

The sponsor's October 2011 resubmission included data from three observational studies examining the effect of topiramate on the 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.

The observational data show that exposure to topiramate, a component of Qsymia, in pregnancy is associated with a 2- to 5-fold increased risk of oral clefts. Data from the North American Anti-Epileptic Drug (NAAED) Pregnancy Registry suggest an estimated 10-fold increase in risk for oral clefts with topiramate.

Additional analyses of clinical data show that Qsymia is associated with small mean increases in heart rate; however, the drug reduces blood pressure resulting in a rate-pressure product (RPP) – a surrogate of myocardial oxygen demand – that is similar between Qsymia and placebo-treated subjects. Analyses of adverse cardiovascular events from the Qsymia phase 2 and 3 clinical trials resulted in few events, but the point estimates of risk for adverse cardiovascular events were all below unity for Qsymia compared with placebo.

The sponsor proposed a risk management strategy that consisted of a [REDACTED] (b) (4) [REDACTED] and a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Medication Guide, a Communication Plan, Elements to Assure Safe Use, an Implementation Plan, and a timetable for submission of assessments of the REMS. The goals of the REMS included:

1. To prevent the potential risk of fetal exposure to topiramate, a component of QNEXA*, by limiting the distribution of QNEXA, contracting with specialty pharmacies, and enrolling prescribers.
2. To inform prescribers, pharmacists, and patients about:
 - i) The potential serious risks associated with QNEXA including teratogenicity and suicidal thoughts and/or behavior; and
 - ii) The appropriate patient selection and the safe-use conditions for QNEXA.

The decision to include the serious risk of suicidal thoughts and/or behavior as part of the REMS was predicated on the Medication Guide-only REMS approved in April 2009 for the antiepileptic drugs, of which topiramate, a component of Qsymia, is a member. However, in June 2011, subsequent to FDA's February 2011 publication of the draft Guidance for Industry: *Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)*, the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) determined "that a REMS is no longer necessary for topiramate to ensure that the benefits of the drug outweigh the risk of suicidal thoughts or behaviors because the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1." Therefore, VIVUS, the sponsor of Qsymia, was advised that the risk of suicidality could be managed through physician and patient labeling, outside of the Qsymia REMS. I will not address this risk further in this document.

DISCUSSION

OND and OSE met internally to discuss the sponsor's proposed REMS for Qsymia; to determine the need for a REMS for Qsymia; and to discuss strategies that could best

* Previous proposed trade name for phentermine/topiramate.

minimize fetal exposures to Qsymia without diverting patients and prescribers to the use of the individual components which are widely available without a REMS in place or planned.

OND and OSE determined that the sponsor's proposal to

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Please see my REMS memo dated July 17, 2012 for the rationale used by OND and OSE in determining that a REMS was necessary to ensure that the benefits of Qsymia outweigh the risks. Among other considerations, OND and OSE had concerns regarding the size and demography of the population likely to use Qsymia. According to NHANES data from 2009-2010, 35.8% of women in the U.S. are obese; the major consumers of weight loss drugs are females of reproductive potential; and in 2009, (b) (4) prescriptions were dispensed from outpatient retail pharmacies for phentermine, a component of Qsymia. Additionally, OND and OSE had concerns about the ability of physician labeling to adequately convey the risk of teratogenicity and ways to mitigate that risk given that healthcare providers likely to prescribe the drug have varying levels of expertise and training. It is anticipated that general practitioners, family practitioners, internists, gynecologists, endocrinologists, cardiologists, and nurse practitioners/physician assistants will all be likely prescribers of Qsymia.

Once a determination was made that a REMS was necessary, OND and OSE sought a reasonable approach to mitigating risk in this situation, where the two components of the combination product are already approved and widely available. OND and OSE believed that a highly restrictive REMS where access to the drug was restricted by safe use conditions (i.e., mandatory pregnancy testing for females of reproductive potential) would increase the use of the separate components for weight loss. If a similarly restrictive REMS were placed on topiramate, barriers to access for patients who use topiramate for other disorders would be created. FDAAA requires that REMS not be unduly burdensome on patient access to the drug. Over 2 million patients receiving topiramate, most of whom are receiving topiramate for seizures or migraine prophylaxis, would be affected by restrictions placed on topiramate use.

OND and OSE believed that a less restrictive REMS that included voluntary prescriber training without restrictions on a prescriber's ability to prescribe or a patient's ability to obtain Qsymia was the preferred option. Both the highly restrictive and less restrictive options were presented to the REMS Oversight Committee (ROC) on December 2, 2011

where unanimous agreement was reached on the less restrictive option. After obtaining ROC concurrence, OND and OSE presented this option to the sponsor. Based on further discussions with the sponsor, OND and OSE agreed on the following proposed REMS to be presented to the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on February 22, 2012 as a reasonable risk mitigation strategy:

1. A Medication Guide for patients that describes the risk of teratogenicity and provides patients with advice regarding safe use of the drug
2. A communication plan targeting prescribers likely to prescribe Qnexa, or its components, for weight loss. The communication plan would support implementation of the REMS, and would reach prescribers who do not opt to receive the training described below.
3. Elements to assure safe use that we propose to include:
 - a. Healthcare providers who prescribe Qnexa will receive training:
The sponsor would be responsible for ensuring that training is available to healthcare providers who choose to prescribe Qnexa; however, the training would not be a requirement for prescribing Qnexa. Training materials would support the risk-benefit discussion with WOCBP, and would provide advice about how to prevent fetal exposures.
 - b. Pharmacies that dispense Qnexa are specially certified:
The sponsor would be required to ensure that only certified pharmacies will dispense Qnexa. Certified pharmacies will be required to provide support to WOCBP, including reminding WOCBP to use contraception, reminding WOCBP to test for pregnancy, and ensuring that the patient receives the Medication Guide. Delivery options for patients to receive Qnexa would likely include shipment of Qnexa to the patients directly by a certified pharmacy or shipment to a pharmacy in the patient's locale for pick-up.
4. An implementation system to ensure pharmacy certification is working as expected
5. A timetable for submission of assessments

While the REMS was not a voting question, EMDAC voted 20-2 to the question:

Considering all the available data included in the application and today's discussions, does the overall benefit-risk assessment of PHEN/TPM support its approval for the treatment of obesity in individuals with a body mass index (BMI) $> 30 \text{ kg/m}^2$ or $> 27 \text{ kg/m}^2$ with weight-related co-morbidities? (VOTING)

- a. *If you voted "Yes" in question #5, please provide your rationale and comment on the approach to post-approval risk management.*
- b. *If you voted "No" in question #5, please provide your rationale and comment on what additional clinical data would be required to support approval.*

The minutes of the EMDAC meeting note the following comments with regard to the proposed REMS:

“committee members agreed that the phentermine/topiramate REMS should capture additional data on long-term adverse events such as heart rate, psychological, cognitive functions, and birth defects. Several members highlighted the need to require treating physicians to be certified prior to treating patients with this agent and that the same requirement should be instituted for dispensing pharmacies.”

The EMDAC’s recommendation to capture additional data on the long-term adverse events cited above will be addressed with post-marketing required clinical studies and trials and enhanced pharmacovigilance.

OND and OSE considered the advice of the EMDAC regarding mandatory physician certification, but continued to believe that such a strategy would divert prescribers to the individual components, thus preventing FDA from getting its risk message out to the indicated population.

Subsequent to the Advisory Committee meeting the sponsor proposed limiting distribution of Qsymia to “a few pharmacies to permit closer monitoring of where the drug is going (prevent internet distribution) and to allow contact with prescribers”. On March 5, 2012, this proposal was taken to the ROC for further discussion; Dr. Woodcock was in attendance at the meeting. The ROC agreed that with the proposal, recommending that the sponsor should be required to use a limited number of certified pharmacies to dispense the drug so as to allow for a “staged introduction” of Qsymia into the marketplace.

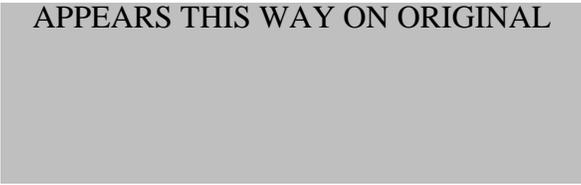
CONCLUSION

OND concurs with OSE that a REMS for Qsymia is necessary to ensure that the benefits of the drug outweigh the increased risk of teratogenicity. The REMS will consist of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of assessments of the REMS. The ETASU will consist of voluntary training for physicians and dispensing of Qsymia through a limited number of mail-order pharmacies. This strategy will provide enhanced educational tools for prescribers and patients, and limited availability to ensure that prescribers prescribing and patients receiving Qsymia have been appropriately informed of:

- the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy
- the importance of pregnancy prevention for females of reproductive potential receiving Qsymia
- the need to discontinue Qsymia immediately if pregnancy occurs

The adequacy of the REMS will be determined by physician and patient understanding of the risk.

APPEARS THIS WAY ON ORIGINAL



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/s/

AMY G EGAN
07/17/2012

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

NDA/BLA #s: 022580
Products: Qsymia (phentermine and topiramate extended-release) Capsules 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, 15 mg/92 mg
APPLICANT: Vivus, Inc.
FROM: Amy G. Egan, M.D., M.P.H.
DATE: July 16, 2012

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

The initial application for Qsymia was submitted on December 28, 2009. Prior to submission of the application, Vivus was advised that a REMS for Qsymia appeared necessary to ensure that the benefits of the drug outweigh the risks of suicidal thoughts or behaviors and, potentially, the risk of teratogenicity. The REMS for the risk of suicidal thoughts or behaviors was predicated on the Medication Guide-only REMS approved in April 2009 for the antiepileptic drugs, of which topiramate, a component of Qsymia, is a member. The sponsor's application included a proposed REMS consisting of a Medication Guide, communication plan, and timetable for submission of assessments of the REMS. On October 28, 2010, a complete response action was taken. In that letter, the sponsor was advised that additional information regarding teratogenic and cardiovascular risks was necessary for the application. To resolve the deficiencies, the sponsor was asked to provide additional data as well as a detailed plan and strategy to evaluate and mitigate the potential risk for teratogenicity or fetal harm in women of child-bearing potential taking Qsymia. The sponsor resubmitted its application on October 14, 2011.

On June 27, 2011, the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) determined that a REMS was no longer necessary for topiramate, a component of Qsymia, to ensure that the benefits of the drug outweigh the risk of suicidal

thoughts or behaviors because the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1.

After consultations between OND and OSE, we have determined that a REMS that includes elements to assure safe use is necessary for Qsymia (phentermine and topiramate extended-release) to ensure that the benefits of the drug outweigh the risk of congenital malformations (specifically orofacial clefts) in infants exposed to Qsymia (phentermine and topiramate extended-release) during the first trimester of pregnancy. In reaching this determination, we considered the following:

- A. Approximately two out of three adults in the United States are considered overweight (BMI 25 to 29.9 kg/m²) or obese (≥ 30 kg/m²). This estimate is based on the 2007-2008 National Health and Nutrition Examination Survey (NHANES) database published in the *Journal of American Medical Association* in January 2010. Phentermine, a component of Qsymia (phentermine and topiramate extended-release), is approved for short-term weight loss and is the most widely prescribed weight loss drug with approximately (b) (4) prescriptions dispensed in outpatient retail pharmacy settings in 2009.
- B. Obesity is associated with numerous co-morbidities, including dyslipidemia, coronary artery disease, hypertension, stroke, and type 2 diabetes mellitus. The second leading modifiable risk factor for death in the United States is overweight.
- C. The benefit of Qsymia (phentermine and topiramate extended-release) is expected based on significant weight loss over lifestyle modification and modest improvements in weight-related co-morbidities. The effect of pharmacological weight-loss on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.
- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the most serious risk of congenital malformation (orofacial clefts) in infants exposed to Qsymia (phentermine and topiramate extended-release) during the first trimester of pregnancy, phentermine and topiramate have been associated with suicidal thoughts or behaviors, increases in heart rate, cognitive-related dysfunction, metabolic acidosis, nephrolithiasis, and acute myopia associated with secondary angle closure glaucoma.
- F. Qsymia (phentermine and topiramate extended-release) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Qsymia (phentermine and topiramate extended-release). FDA has determined that Qsymia (phentermine and topiramate extended-release) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Qsymia (phentermine and topiramate extended-release). FDA has determined that Qsymia (phentermine and topiramate extended-release) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware

because information concerning the risks could affect patients' decisions to use, or continue to use Qsymia (phentermine and topiramate extended-release).

The elements of the REMS will be a Medication Guide, elements to assure safe use, including that healthcare providers who prescribe Qsymia (phentermine and topiramate extended-release) will be specially trained, and pharmacies that dispense Qsymia (phentermine and topiramate extended-release) will be specially certified, an implementation system, and a timetable for submission of assessments of the REMS.

The elements to assure safe use (ETASU) will allow for ongoing education for prescribers on the teratogenic risk associated with the use of Qsymia (phentermine and topiramate extended-release) and ways to mitigate that risk, including counseling females of reproductive potential on the need to have monthly pregnancy testing performed, and on the need to use acceptable forms of contraception while taking Qsymia (phentermine and topiramate extended-release), and what are considered acceptable forms of contraception. The ETASU will also serve to inform patients of the teratogenic risk of Qsymia (phentermine and topiramate extended-release), through a Medication Guide and a patient brochure, and ways to mitigate that risk, including having monthly pregnancy testing performed and using acceptable forms of contraception while taking Qsymia (phentermine and topiramate extended-release), and educating them as to what are considered acceptable forms of contraception.

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/s/

AMY G EGAN
07/17/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

**Interim Comments on Risk Evaluation and Mitigation Strategy (REMS)
Set # 2**

Date: May 16, 2012

Reviewer(s): Joyce Weaver, Pharm.D., Risk Management Analyst
Kate Oswell, M.A., Health Communications Analyst
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Drug Name(s): QNEXA (phentermine and topiramate extended-release)

Therapeutic Class: Combination comprising an anti-epileptic and a
sympathomimetic amine anorectic

Dosage and Route: 3.75 mg phentermine/23 mg topiramate orally daily for 14
days, then 7.5 mg phentermine/46 mg topiramate orally
daily

Application Type/Number: 022580

Submission Number: REMS submissions received April 4, 2012 and April 12,
2012; DARRTS documents # 84, 88

Applicant/sponsor: Vivus, Inc

OSE RCM #: 2011-4184

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1 INTRODUCTION

The following are regulatory milestones pertinent to the REMS for Qnexa:

- December 28, 2009—NDA 022580 submitted for Qnexa (now tentatively named Qnexa), phentermine/topiramate capsules.
- July 15, 2010—the application was considered by the Endocrine and Metabolic Drugs Advisory Committee; the committee voted 10-6 recommending against approval of the application.
- October 28, 2010—a complete response (CR) action was taken on the application submitted December 28, 2009 citing a need for a comprehensive assessment of topiramate's and phentermine/topiramate's teratogenic potential, and evidence that the elevations in heart rate associated with phentermine/topiramate do not increase the risk for major adverse cardiovascular events.
- October 17, 2011—the NDA was resubmitted; the resubmission included a REMS submission.
- February 22, 2012—the resubmitted application was considered by the Endocrine and Metabolic Drugs Advisory Committee; the committee voted 20-2 recommending approval of the application.
- March 21, 2012—the FDA and the applicant met to discuss the REMS; REMS interim comments set #1 was prepared by the FDA for this face-to-face meeting.
- April 4, 2012—applicant submitted a REMS proposal based on the REMS outlined at the February 22, 2012 advisory committee meeting and the March 21, 2012 face-to-face meeting.
- April 6, 2012—FDA notified the applicant that the April 4, 2012 submission constituted a major amendment; the user fee goal date was extended to July 17, 2012.

2 MATERIALS REVIEWED

- REMS proposal in submissions of April 4, 2012 and April 12, 2012

3 SUMMARY OF APPLICANT'S PROPOSED REMS

The goal of the proposed REMS is to inform prescribers and females of childbearing potential about the following: the risk of congenital malformation associated with fetal exposure to Qnexa during pregnancy, the importance of pregnancy prevention, and the

need to minimize fetal exposure. The REMS elements include a Medication Guide, elements to assure safe use (healthcare providers who prescribe Qnexa will be specially trained, pharmacies that dispense Qnexa will be specially certified), an implementation system, and a timetable for submission of assessments (6 months, 12 months, and then annually from the date of the initial approval of the REMS). The training for prescribers includes a training module that can be completed in-person, administered by medical liaison, via an online training module, or through completion of a hardcopy printed training module.

The assessment reports will include assessment of patient and healthcare prescribers (HCP) understanding of the teratogenic risk of Qnexa, distribution data regarding the Dear Healthcare Professional letter, data regarding completion of HCP training, review and critique of training strategies, data from certified pharmacies regarding the patients who are receiving Qnexa, data from certified pharmacies regarding prescribers, data regarding adherence to distribution and dispensing requirements, and evaluation of the extent to which the REMS is meeting its goals.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Qnexa REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for Qnexa. Appended to this review are the REMS proposal, REMS materials, and the REMS supporting document, including our track changes. The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document. Because labeling negotiations have not been completed, the applicant should be reminded that the REMS proposal, REMS materials, and the REMS supporting document will need to be consistent with the final labeling.

5 COMMENTS FOR THE APPLICANT

5.1 ELEMENTS TO ASSURE SAFE USE

The information regarding the training of non-prescribing healthcare personnel should be removed from the REMS document and placed in the REMS Supporting Document:

REMS-related training will also be made available to office staff and non-prescribing healthcare personnel to assist in patient counseling and care; however, since these personnel do not have DEA#s they will not be tracked in the database.

The continuing medical education (CME) portion of the proposed REMS, the defined REMS curriculum for CME providers (Appendix D), should be removed from the REMS and placed into the REMS Supporting Document. The CME portion of the REMS cannot be developed until the FDA develops a blueprint for the CME. The planned CME program should be placed in the REMS Supporting Document as a future enhancement to the REMS.

5.2 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Note the edits to the wording of this section of the REMS.

5.3 COMMENTS FOR THE APPLICANT ON REMS MATERIALS AND DOCUMENTS

DHCP Letter

See Dear Healthcare Provider letter (attached) for suggested track changes.

Dear Medical Society Letter

Changes to this letter should reflect changes made to the Dear Healthcare Provider Letter.

Provider Education (website screen shots)

Healthcare providers have to scroll down each page to read all information in the program. This is not user friendly for the presentation of the educational information. Website screen shots for the education program should look more like the provider education slides, with all information on each slide being presented on the screen. Instead of scrolling down, providers should simply click a next button to get to the next slide. We recommend replacing the current presentation of the information in the education program on the website to look more like the provider education slides.

Remove the

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Add a link to the ISI at the bottom of the screen, as you have done with the Full Prescribing Information and Medication Guide during the presentation of the education program material.

Provider Education (slides available online)

A voice track should accompany the presentations for electronic training. Submit the script for the voice track for Agency review.

Each electronic training module should inform the HCP the expected time needed to complete the training module.

Slide 1: Replace (b) (4) with "Training Program" throughout to be consistent with the language in the REMS.

Correct the capitalization on the given name of the drug (phentermine and topiramate extended-release)

Include the term "teratogenic" when describing risk in the Overview "...to educate healthcare providers about the **teratogenic** risks associated with Qnexa therapy for the treatment of obesity."

Replace goals with (b) (4) of the REMS: "The (b) (4) of the REMS is to inform prescribers and females of reproductive potential (FRP) about the:

- Increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qnexa during during the first trimester of pregnancy
- Importance of pregnancy prevention

3 Pages Of Draft REMS Have Been Withheld In Full
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5.4 GENERAL COMMENTS FOR THE APPLICANT

- All REMS materials must reflect the final approved labeling.
- We use the new name throughout these comments. All documents and materials should be changed to reflect the new name of the product.
- Replace the term [REDACTED] ^{(b) (4)} to “females of reproductive potential” on all materials.
- Change the definition of a female of reproductive potential to include “never having had a hysterectomy (uterus removed), surgical sterilization (tubes tied), or both ovaries removed, and not going through menopause. Menopause should be confirmed by a healthcare provider.
- Change name of the [REDACTED] ^{(b) (4)} to “Risk of Birth Defects with Qnexa for Females Who can Become Pregnant.”

- Unless specifically stated, formatting changes are inadvertent due to conversion of documents from PDF to WORD to track changes.
- Make the following changes to the Important Safety Information (ISI) in all materials where the ISI is presented.
 - The phrase [REDACTED] (b) (4) minimizes this risk by omitting important material information from the draft PI. Revise to read “Take Qnexa once daily in the morning with or without food.after 14 days increase dose to Qnexa 7.5mg /46 mg.”
 - The phrase [REDACTED] (b) (4) minimizes the risk of elevated heart rate by disassociating the risk from Qnexa. Revise this phrase to “Qnexa has been associated with an increase in heart rate.”

We have created a concept showing the birth control options for patients, as well as the acceptable forms of birth control for healthcare providers. We recommend using these concepts in the patient and prescriber materials as appropriate, to explain the acceptable forms of birth control, replacing the current contraception charts. VIVIS should use the options concept as shown, but create a user friendly design (e.g., using colors, layout, formatting) that makes the charts easy to follow and will match the look and feel of your current program materials

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Qnexa with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

The REMS has not completed the clearance process, therefore additional changes maybe necessary.

6 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document.

Include information in the REMS Supporting Document about how Vivus will triage REMS questions received from stakeholders.

ATTACHMENTS

Draft REMS, REMS materials, and REMS Supporting Document with track changes

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

/s/

JOYCE P WEAVER
05/16/2012

CYNTHIA L LACIVITA
05/17/2012
Concur

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

REMS OPTIONS REVIEW

Date: August 10, 2010; *Revised October 11, 2010*

To: Mary H. Parks, M.D., Director
Division of Metabolic and Endocrinologic Drug Products
(DMEDP)

Through: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)

From: QNEXA (Phentermine/Topiramate) REMS Review Team

Scientific Lead: Carolyn L. Yancey, M.D., F.A.A.P.,
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Marcia Britt, Ph.D., Health Education Reviewer, DRISK

Gita Toyserkani, Pharm.D., M.B.A., Acting Team Leader,
DRISK

Subject: Risk Evaluation and Mitigation Strategy (REMS) Options

Trade/Established Name: QNEXA (Phentermine and Topiramate)

Therapeutic Class: Appetite Suppressant (Phentermine: synthetic sympatho-
mimetic amine appetite suppressant. Topiramate: neuro-
therapeutic anti-epileptic)

Strength, Dosage Form: PHEN/TPM: low-dose 3.75 mg/23 mg; mid-dose 7.5 mg/
46 mg; three-quarter dose 11.25 mg/69 mg; and high-dose
15 mg / 92 mg; Controlled-Release Capsules

Application Type/Number: NDA 022-580

Applicant: VIVUS, Inc.

OSE RCM #: 2010-130

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EXECUTIVE SUMMARY

This Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) review evaluates possible risk evaluation and mitigation strategy (REMS) options for QNEXA (phentermine/topiramate, PHEN/TPM) in the context of five risks in the PHEN/TPM clinical trials for obesity: psychiatric adverse events (AEs) including depression and suicidality, neurocognitive AEs including difficulty with attention and cognitive function, cardiovascular (CVS) AEs including tachycardia and decreased blood pressure, metabolic acidosis, and associated teratogenic risk of fetal exposure to TPM.

DMEP and DRISK concur that the risk of suicidality and the associated teratogenic risk with TPM warrant mitigation under REMS for QNEXA and that the other three risks (CVS, neurocognitive, and metabolic acidosis events) with QNEXA can be managed with labeling and a postmarketing observational outcomes study.

The applicant submitted a REMS proposal that includes a Medication Guide and a communication plan to address the risks of suicidality and teratogenicity. The applicant also proposed additional tools, some of which, if required, would be under an element to assure safe use (ETASU).

DRISK believes a Medication Guide is sufficient to address the risk of suicidality in the absence of evidence that the risk of suicide is augmented with QNEXA above the AED class risk for suicide. With regard to the potential teratogenic risk, DRISK believes that ETASU cannot be ruled-out for a QNEXA REMS based on the probable widespread usage, if approved, in females of child-bearing potential (FCBP). The final decision should also be based upon risks associated with use of QNEXA for the population it is likely to be used in. This decision cannot be made outside the context of burden and feasibility relative to the two component products availability. Therefore, we recommend a fuller discussion of the risk of teratogenicity with PHEN/TPM as well as the elements that would be required in the QNEXA REMS at a Center Director Briefing and possibly a future advisory committee meeting.

1 INTRODUCTION

QNEXA® is a fixed-dose, combination product with two active ingredients, immediate-release PHEN hydrochloride beads and modified-release TPM beads for oral administration. Phentermine hydrochloride is available in the United States (US) under the trade name Adipex-P™ and the generic name of Phentermine hydrochloride in oral capsule and tablet forms in multiple strengths. Topiramate is available in the US under the trade name Topomax™ and the generic name, topiramate, in oral capsule and tablet forms in multiple strengths.

QNEXA controlled-release capsules are proposed in four dose strengths (PHEN/ TPM): low-dose 3.75 mg/23 mg; mid-dose 7.5 mg/46 mg; three-quarter dose 11.25 mg/69 mg; and high-dose 15 mg/92 mg), are differentiated by color, [REDACTED] (b) (4)

REMS Proposal

The applicant submitted a REMS proposal for QNEXA (original submission December 28, 2009) based on the Agency's request for REMS (see Section 1.2, Regulatory History, Type-B, Pre-NDA Meeting July 22, 2009, in this review) focused on the risk of suicidal ideation with TPM in QNEXA. The original REMS proposal for QNEXA includes goals, a Medication Guide, and timetable for submission of assessments. An amended REMS proposal (submitted May 24, 2010; and August 9, 2010) includes the addition of a communication plan. The proposed communication plan includes a Dear Healthcare Provider (DHCP) letter and on-line education

training for HCPs about risks associated with use of QNEXA. In this amended REMS proposal, the applicant expands risks for mitigation under the REMS to include suicidal ideation *and* the associated teratogenic risk of fetal exposure to TPM. A detailed description of the REMS proposal is included in Section 4 of this review.

1.1 BACKGROUND

This New Drug application (NDA), 022-580, is submitted under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) and is based, in part, on the Agency's previously determined safety for separately approved products, PHEN and TPM. The combination of PHEN/TPM (VI-0521) clinical development program is submitted by the applicant in support of efficacy and safety of VI-0521 for treatment of obesity in adults, including weight loss and maintenance of weight loss, used in conjunction with diet and exercise in adults. QNEXA is indicated for treatment of obesity, including weight loss and maintenance of weight loss and should be used in conjunction with diet and exercise.

The applicant's rationale for the QNEXA clinical development program in obesity is based on the widespread concern about the growing population of obese adults in the US. Per the applicant's rationale, the National Health and Nutrition Examination Survey indicate that approximately 66% of adults in the US are obese or over-weight.¹ Obesity is associated with numerous co-morbidities, including dyslipidemia, coronary artery disease, hypertension, stroke, and Type 2 diabetes.² Moderate weight loss of 5% to 10% can result in a marked reduction in obesity-related metabolic and cardiovascular risk factors.³

Phentermine hydrochloride was approved by the Food and Drug Administration (FDA) in 1959 as an appetite suppressant for short-term (a few weeks) weight loss in adults at doses of 15, 30, and 37.5 mg/ day. Currently, PHEN is the most widely-prescribed weight-loss drug. Phentermine is not approved for any indication in children < 16 years of age. Phentermine is available as Adipex-P tablets approved by FDA October 1980 and capsules approved August 1983. Various PHEN products are available as generics.

Topiramate (Topamax™) was approved in 1996 as an AED for monotherapy of epilepsy in adults. Topiramate is approved for:

- 1) initial monotherapy in patients ≥ 10 years of age with partial onset or primary generalized tonic-clonic seizures (200 to 400 mg/day in two divided doses),
- 2) as adjunctive therapy for adult and pediatric patients (2 to 6 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥ 2 years of age with Lennox-Gastaut syndrome,
- 3) treatment in adults for prophylaxis of migraine headache.

In 2004, TPM was approved for prophylaxis of migraine headache in adults (100 to 200 mg/day divided into two doses).

On December 16, 2008, FDA issued a letter to all sponsors of approved AEDs to request safety

¹ Ogden CL, Carroll MD, Curtin, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549-1555.

² Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. Arterioscler Thromb Vasc Biol 2006; 26:968-976.

³ Goldstein DJ, Beneficial health effects of modest weight loss. Int J Obes Relat Metab Disord 1992; 16:397-415.

labeling changes including a Medication Guide and a REMS to inform patients of the increased risk of suicidal ideation and behavior. Those labeling changes were approved on December 22, 2009. The Topomax REMS was approved on April 23, 2009.

1.2 REGULATORY HISTORY

The regulatory history that relates to the QNEXA REMS proposal is briefly summarized below:

-  (b) (4)
- Type-C Guidance Meeting (March 16, 2006): In regard to TPM pregnancy risks and the recommended pregnancy category for an indication in obese adults, the Agency explains that, “most anti-epileptic drugs, including topiramate, are labeled pregnancy category C, based on the risk/benefit profile. However, the findings of embryo-lethality and teratogenicity with topiramate in all species would warrant a pregnancy category X designation of the less serious indications such as obesity.”
- Type-B, End-of Phase 2 Meeting (May 2, 2007): Topiramate doses used in the PHEN/TPM clinical development program are less likely to alter estrogen levels than the higher doses used to treat seizure disorders. The Agency recommends that all women taking estrogen-containing oral contraceptives, upon study entry, be made aware that TPM may reduce the efficacy of oral contraceptives and be told to report significant changes in their bleeding patterns to the investigative physician.
- Peripheral and Central Nervous System Drugs/Psychopharmacologic Drugs Advisory Committee Meeting (July 10, 2008): This advisory committee convened to discuss reports of treatment-emergent suicidality (suicidal ideation and behaviors) with AEDs in studies of epilepsy. The Committee agreed there is significant risk of suicidality and voted in favor of adding Warnings and Precautions about suicidality to all AED labeling to better inform patients of the increased risks of suicidal ideation and behavior. The Agency concluded that there is a signal for increased suicidality for the Class of AEDs and ordered product labeling for all chronically used AEDs describe this increased risk. A Medication Guide, but no Boxed Warning, was ordered by FDA.
- FDA Warning (December 16, 2008): New safety information is provided to patients and healthcare professionals to alert them to an increased risk of suicidal thoughts and behaviors, defined as suicidality, in patients who take antiepileptic drugs to treat epilepsy, bipolar disorder, migraine headaches, and other conditions. Under the authority of FDAAA, the Agency required manufacturers of AEDs to add a warning to their product prescribing information about the increased risk of suicidality in the form of a Medication Guide.
- AED Labeling Changes (December 22, 2009): AED labeling including a Medication Guide was approved by FDA.
- REMS for Topomax (April 23, 2009): Approved by FDA.
- Type-B, Pre-NDA Meeting (July 22, 2009): The Agency recommends that the applicant submit a REMS proposal including, at a minimum, a Medication Guide and timetable for submission of assessments. Whether or not additional REMS elements will be required is a review issue.

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

An Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC) was held July 15, 2010 to discuss QNEXA for treatment of weight loss in obese (BMI \geq 30 kg/m²) or overweight (BMI \geq 27 kg/m²) individuals with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity. The committee voted 10 - no, 6 - yes, and 2 - abstentions to the Agency's question, "based on the current available data, do you believe the overall benefit-risk assessment of PHEN/TPM (QNEXA) is favorable to support its approval for the treatment of obesity patients with a BMI \geq 30 kg/m² or \geq 27 kg/m² with weight-related co-morbidities?"

When asked whether risk management measures should be applied to QNEXA, if approved, the committee expressed concern that any risk management with QNEXA will be difficult due to the wide-spread use of weight loss products. Many committee members voiced desire for "tight control" or a "staged-launch" prescribed by only endocrinologists or physicians who manage weight-loss clinics. The committee articulated, even with a limited prescriber network, that it may not be feasible to employ a patient registry or provider registry because weight loss drug utilization is reported in millions of prescriptions. Though ETASU were minimally mentioned, committee members recommended patient /prescriber registry with the same caveats discussed above. There was no mention of a restricted distribution program for access to QNEXA (see **Appendix A** for a complete summary of the EMDAC discussion).

2 MATERIAL REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following resources were reviewed:

- December 28, 2009: Original REMS proposal for QNEXA is submitted with the original NDA 22580.
- May 24, 2010 *: Amended REMS with communication plan is submitted; includes recommendation for a long-term large outcomes trial to assess CVS events with PHEN/TPM (submitted as Amendment 0036, Risk Management Plans, August 9, 2010).
- June 21, 2010: Applicant's QNEXA Briefing Document for EMDAC is submitted.
- August 3, 2010 *: Amended REMS "QNEXA Focused Launch and Assurance for Safe Use Program Overview" is submitted (Amendment 0036, Risk Management Plans, August 9, 2010).
- August 9, 2010 *: As noted above for May 24 and August 3, 2010.

Prescribing Information

- December 28, 2009: Annotated QNEXA™ labeling.
- December 2009: TOPOMAX® Prescribing Information.

FDA Reviews

- Pediatric and Maternal Health Team Review for QNEXA, NDA 22580, Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst; Medical Team Leader, Karen B. Feibus, M.D., June 2, 2010.

- OSE, Division of Epidemiology, Drug Utilization Review for Phentermine Concurrency with Topiramate, Vicky Borders-Hemphill, Pharm.D., Drug Use Data Analyst; Drug Use Analyst Team Leader, Laura Governale, Pharm.D., M.B.A., June 7, 2010.

FDA Guidance Documents

- Draft Guidance for Industry:
 - Developing Products for Weight Management, February 2007
 - Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications, September 2009.
 - Prospective Assessment for Suicidality in Clinical Trials of Products Being Developed for Psychiatric Indications (August 5, 2010)

2.2 ANALYSIS TECHNIQUES

The amended QNEXA REMS is reviewed to determine the following:

- The possible REMS options that could be considered for QNEXA, if approved, and the rationale, including the advantages and limitations for each option based on risks to be mitigated under QNEXA REMS, specifically, suicidality and associated teratogenic risk with fetal exposure to TPM.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF THE CLINICAL PROGRAM

The PHEN/TPM clinical database (original submission December 28, 2009) consists of 549 healthy subjects and 57 patients with either hepatic or renal impairment from 10 completed Phase 1 clinical trials; 490 subjects from four completed Phase 2 clinical trials [OB-201, OB-202, DM-230 (28-week extension of Study OB-202), and DM-231 (52-week, open-label extension of Study DM-230)], and 4,510 subjects from three pivotal completed Phase 3 clinical trials (OB-301, OB-302, OB-303). *Note: Study DM-231 was terminated after 16 weeks per FDA recommendations that the study data would not be interpretable due to lack of a control group.*

Efficacy

The three pivotal Phase 3 clinical trials (OB-301, OB-302, and OB-303) form the basis for the PHEN/TPM efficacy analyses based on 12 month exposure data. Study OB-301 is a randomized, double-blind, placebo-controlled, multicenter, factorial trial in obese adults that compared high-dose and mid-dose PHEN/TPM with PBO and the respective single-agents, PHEN and TPM components, after 28 weeks of treatment. Study OB-302 and OB-303 are both randomized, double-blind, placebo-controlled, 56-week trials. Each trial includes a 4-week titration phase.

The demographic characteristics for Study OB-302 and OB-303 are similar: the majority of subjects were women (74%), Caucasian (84%) with an average age of 45 years; elderly subjects (≥ 65 years) are less than 8% of all subjects and the majority of subjects are extremely obese, ≥ 40 kg/m². Clinical trial completers were 53%, 57%, 69%, and 62% in PBO, low-dose, mid-dose, and high-dose treatment groups, respectively.

Primary Efficacy Variables and Efficacy Results

The co-primary efficacy variables for the Phase 3 studies were the percent weight loss and the percent of patients with at least 5% weight loss. The primary endpoint is the last observation carried forward (LOCF) for Study OB-301 at Week 28 and LOCF for Study OB-302 and OB-303

at Week 56. The Intent-to-Treat (ITT) LOCF analyses includes patients that were off study drug at their last study visit. There are statistically significant dose-related reductions in percent body weight, baseline to Week 56, in all PHEN/TPM-treated groups relative to PBO. In a categorical analysis, 20% of PBO-treated subjects lost $\geq 5\%$ baseline body weight following one year of treatment versus 45%, 62%, and 69% weight loss with low-dose, mid-dose, and high-dose PHEN/TPM-treatment, respectively. PHEN/TPM-treatment groups demonstrated improvements in blood pressure, lipids, and glycemia. Only high-dose PHEN/TPM-treatment demonstrates statistical significance in improvement in subgroup analyses of weight-related co-morbid conditions.

Based on the Draft Guidance for Industry: Developing Products for Weight Management (February 2007), low-dose, mid-dose, and high-dose PHEN/TPM are efficacious for weight loss in obese adults as defined by the applicant. The applicant did not study three-quarter PHEN/TPM dose (11.25 mg/69 mg) in the Phase 3 clinical trials; this dose strength is for titrating.

3.2 SAFETY CONCERNS

The PHEN/TPM clinical safety database is based on 12-months exposure as summarized by treatment group (**Table 1**). The PHEN/TPM mean exposure in the 1-year cohort is 286 days and median exposure is 390 days. In total, 1,511 (65%) of patients on PHEN/TPM and 862 (55%) of PBO patients have more than 52 weeks exposure to PHEN/TPM.

Table 1.

Extent of Exposure to PHEN/TPM – 12 Month Clinical Safety Database						
	PBO	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92	PHEN/TPM Total*	Total*
Extent of Exposure (days) n	n = 1561	n = 240	n = 498	n = 1580	n = 2318	n = 3879
(%) Exposed > 52 wks and \leq 56 wks	n = 398 (26%)	n = 55 (23%)	n = 167 (34%)	n = 458 (29%)	n = 680 (29%)	n = 1078 (28%)

The safety assessment of PHEN/TPM includes five key risks as stated in the Executive Summary of this review.

3.2.1 TERATOGENICITY

The risk of teratogenicity associated with exposure to TPM is one of the key risks in the PHEN/TPM clinical development program. Based on three non-clinical reproductive toxicity studies, TPM is associated with harmful fetal effects. A brief summary of TPM animal studies follows:

- **Mice Studies:** When oral doses of 20, 100 or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) increased at all doses.
- **Rat Studies:** With oral doses of 20, 200, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) increased among offspring of dams treated with 400 mg/kg [10 times the recommended human dose (RHD) on a mg/m² basis] or greater during the organogenesis period of pregnancy.

- Rabbit Studies: With 20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis, embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m² basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m² basis).

The applicant completed embryo fetal development studies in rats and rabbits with PHEN/TPM and reports no observed drug-induced effects. These studies were not designed to assess fetal toxicity at higher doses of TPM although PHEN/TPM exposures in rats and rabbits were approximately equal to the proposed PHEN/TPM doses.

Topiramate-exposed human pregnancy outcomes are tracked in the North American AED Pregnancy Registry, the United Kingdom (UK) Epilepsy and Pregnancy Registry, and the FDA Adverse Event Reporting System (AERS). The TPM pregnancy outcomes are summarized:

North American Antiepileptic Registry (2010 Annual Report, unpublished)

- 296 participants, (85% epilepsy) show higher prevalence of TPM fetal exposed infants with malformations (4.1%, 95% CI: 1.9, 7.6) compared with controls (1.6%, 95% CI: 1.5, 1.7), 11 major malformations including 4 oral cleft abnormalities, 2 limb abnormalities.

UK Epilepsy and Pregnancy Registry

- Among 70 TPM monotherapy exposed pregnancies, 3 major malformations (5%, 95% CI: 1.7, 13.3) are reported: 2 oral cleft abnormalities with TPM, 200 mg/day and 800 mg/day; 1 hypospadias at 600 mg/day. No control groups exist for these data; the duration of exposure is unknown.

FDA Adverse Event Reporting System (AERS)

- 115 cases of TPM exposure in pregnancy (39 excluded; Of the 76 cases analyzed:
 - 51 included a diagnosis for use, of these 47 (92%) include epilepsy diagnosis and 4 cases include concomitant medications: Carbamazine (2 cases), Lamotrigine, and radiation/chemotherapy exposure, (1 case) each
 - 45 of 76 cases analyzed, 64% of doses ≤ 200 mg/day; 40 of 46 cases (87%), that include timing of fetal exposure, include exposure in the 1st trimester.
 - Congenital malformations are reported in 71 of 76 (93%) cases; 7% postnatal AEs are without malformations.
 - 67 total reported AEs with TPM monotherapy (excluding 4 genetic syndromes; 5 post-natal AEs without malformations); 3 malformations not specified; 64 malformations associated with TPM monotherapy:
 - ❖ Craniofacial malformations, 21 of 64 (33%): 11 cleft lip/palate, 6 facial dysmorphism including auricular dysplasia, 4 micrognathia, 3 skull deformities, ossification abnormalities, 1 macroglossia.
 - ❖ Skeletal malformations, 19 of 64 (30%): 16 limb malformations, 8 phalangeal (brachydactyly, adactyly, syndactyly), 5 long bones (radius, femur, hypoplasia, deformity), 6 hip dysplasia, talipes equino deformities, 4 vertebral.
 - ❖ Cardiovascular malformations 15 of 64 (23%): 11 ventricular or atrial septal defect, one each - single ventricle, patent ductus arteriosus (PDA), pulmonary artery stenosis, aortic hypoplasia, bicuspid aortic valve, and transposition of the great arteries.

The pattern of human congenital malformations reported in AERS is similar to the pattern of malformations reported in animal studies. The AEs with TPM doses \leq 200 mg/day are not different compared with higher TPM doses \geq 400 mg/day.

The FDA reports low birth weight ($<$ 2500 g) associated with TPM from an abstract (Hernandez-Diaz presented at the Teratology Society Meetings, June 2010) and a RR of 2.7 (95% CL: 1.4 to 5.1). In this abstract, the TPM-exposed group has two controls: age-matched family/friends and a larger child-bearing population. In AERS data, a total of 64 TPM exposed pregnancies are associated with malformations reported as craniofacial malformations, 21 of 64 (33%), 11 of 21 as cleft lip and or palate; skeletal malformations, 19 of 64 (30%); and cardiovascular malformations, 15 of 64 (23%).

Prospective Cohort Study

In a controlled prospective cohort study comparing 98 women treated with FEN/PHEN compared with 233 women not treated with FEN/PHEN, the proportion of live born infants with major structural anomalies was similar in the two groups (3.6% versus (vs) 1.0%, RR 3.59; 95% CI 0.61, 21.10) as was the proportion of infants with \geq 3 minor anomalies (11.7% vs 7.6%, RR 1.53; 95% CI 0.61, 3.82). No pattern of malformation was identified. There were no significant differences between the groups with spontaneous pregnancy loss (6.1% vs 8.2%, $P = 0.65$) or premature delivery (8.6% vs 7.7%, $P = 0.95$). Although it is not possible to rule out weak to moderate associations, lack of an increased risk of spontaneous pregnancy loss and of major or minor anomalies in offspring of women who took FEN/PHEN during the first trimester of pregnancy is reassuring.⁴

Pregnancy Outcomes in PHEN/TPM Clinical Trials

The average gestational age among 34 reported pregnancies was 5.4 weeks at pregnancy diagnosis; 13 of 34 pregnancies occurred during oral contraceptive use. Nineteen of 34 pregnancies delivered without major malformations. There were 6 elective terminations, 6 spontaneous terminations, 1 ectopic pregnancy, 1 unknown outcome and 1 lost to follow-up.

Possible explanations for pregnancies in PHEN/TPM clinical trials are:

- 1) Improper use or lack of use of required appropriate birth control methods;
- 2) Weight-loss, in-and-of-itself, is associated with increased fertility; and
- 3) Drug-drug interaction study that demonstrates decreased oral contraceptive efficacy in patients taking PHEN/TPM concomitantly with oral contraceptives containing estrogen. The drug-drug interaction study involved co-administration of PHEN/TPM (15/92 mg) with a single oral contraceptive containing, for example, 35 μ g ethinyl estradiol and 1 mg norethindrone. The finding demonstrated a decreased the area under the curve (AUC) of norethindrone estradiol by 16% and increased in the C_{max} and AUC of norethindrone by 22% and 16%, respectively. It is noteworthy that the applicant did not complete a pharmacodynamic study with QNEXA and oral contraceptives.

3.2.2 PSYCHIATRIC-RELATED ADVERSE EVENTS

The risk of suicidality is one of the key risks in PHEN/TPM clinical trials for QNEXA. Psychiatric AEs with AEDs are well characterized including the risk suicidal behavior and ideation. In a meta-analysis of 199 PBO-controlled trials across 11 approved AEDs, FDA reports

⁴ Jones KL, Johnson KA, Dick LM, Felix RJ, Kao KK, Chambers CD. Pregnancy Outcomes After First Trimester Exposure to Phentermine/Fenfluramine, TERATOLOGY 2002,65:125-130.

an odds ratio of 1.8 for suicidal thoughts and behavior (95% CI: 1.2, 2.7) for patients treated with an AED compared with PBO. These data are based on retrospective assessment of patient-reported AEs (see FDA AC, 2008, Suicidality and AEDs).

In PHEN/TPM clinical trials, 4 to 7 times as many patients randomized to high-dose PHEN/TPM versus PBO discontinued a clinical trial due to a psychiatric AE. A brief summary of psychiatric events follows:

- 1) Anxiety-related AEs as depression are reported with almost 3 times as many events with high-dose PHEN/TPM treatment compared with PBO treatment.
- 2) Depression-related AEs are reported as 3%, 5%, 4%, and 8% in PBO, low-dose, mid-dose, and high-dose PHEN/TPM-treatment groups, respectively. Depression is reported as 6 times the incidence (1.3) with high-dose PHEN/TPM group compared with PBO (0.2).
- 3) Sleep-related disorder AEs are reported as 6%, 7%, 7%, and 11% of patients in PBO, low-dose, mid-dose, and high-dose PHEN/TPM-treatment groups, respectively. Insomnia is reported as 4-times the incidence (1.6) with high-dose PHEN/TPM compared with PBO (0.4) and mid-dose PHEN/TPM (0.4) treatment.

The incidence of suicide ideation or behavior assessed with the Columbia Suicidality Severity Scale (C-SSRS) questionnaire demonstrates 11 (0.7%) PBO-, 1 (0.4%) low-dose, 3 (0.6%) mid-dose, and 14 (0.9%) high-dose PHEN/TPM-treatment groups. Three episodes of suicide ideation are reported: one PBO-treated patient (Day 194), and, one patient each, with low-dose PHEN/TPM-treatment (Day 47) and with high-dose PHEN/TPM-treatment (Day 24). The EMDAC conveyed significant concern about the C-SSRS results with events of “suicidality (behavior or ideation)” and “any suicidal ideation” though no completed suicides are reported with PHEN/TPM, to date.

The EMDAC underscored FDA’s experience with rimonabant, a cannabinoid receptor blocker in the brain proposed for two indications: 1) an appetite suppressant and 2) treatment for smoking cessation. The rimonabant EMDAC (July 13, 2007) voted not to recommend approval until further risk assessment could be completed. The FDA required Sanofi-Aventis to complete a large, long-term outcome study of rimonabant in obese patients to better characterize psychiatric events based on early clinical trial data suggesting increased rates of depression and anxiety. Based on results from the outcome study, rimonabant was not approved by FDA due to serious risk of severe depression possibly leading to suicidality and development of neurodegenerative diseases (Multiple Sclerosis, Parkinson’s disease, Alzheimer’s disease, and Huntington’s disease). Rimonabant was taken off the market in Europe in October 2008.

3.2.3 NEUROCOGNITIVE DYSFUNCTION ADVERSE EVENTS

In PHEN/TPM clinical trials, patients treated with PHEN/TPM report increased cognitive-related AEs compared with PBO-treated patients. Neurocognitive AEs include increased events of confusion, attention, memory impairment, and difficulty with speech/language with PHEN/TPM compared with PBO-treated patients. With TPM monotherapy in epilepsy and migraine, AEs are most frequently related to the central nervous system (CNS). The increased incidence of cognitive-associated AEs, including confusion, psycho-motor slowing, difficulty with concentration, attention, memory, and speech and language problems are reported with TPM (100 mg to 400 mg/day) in migraine headache (adults) and treatment of seizures (adults and children).

In PHEN/TPM clinical trials, cognitive disorder AEs include attention disorder, memory impairment, and language disorder, and demonstrate a dose-related increase in these AEs with

PHEN/TPM, in particular, with the high-dose. High-dose PHEN/TPM-treated patients are at 5 times-, 4 times-, and 10 times-greater risk to experience attention, memory impairment, and language AE with low-dose, mid-dose and high-dose PHEN/TPM, respectively, compared with PBO-treated patients. The AEs of attention, memory, language, and other cognitive disorders, show pooled incidence rates as 2%, 2%, 6%, and 8% in PBO, low-dose, mid-dose, and high-dose PHEN/TPM-treatment groups, respectively. Though these outcomes are not powered for statistical significance and these incidence rates are small, the clinical significance remains a concern.

3.2.4 METABOLIC ACIDOSIS

Metabolic acidosis (hyperchloremic, anon-anion gap) is a risk with PHEN/TPM due to the inhibitory effect of TPM on carbonic anhydrase causing loss of renal bicarbonate. The TPM labeling cites “bicarbonate decrements are usually mild-to moderate (average decrease of 4 mEq /L with a TPM dose of 400 mg/day in adults).

The percentage of patients who experienced two consecutive or an endpoint bicarbonate value < 21 mEq/L are 2%, 9%, 6%, and 13% in PBO, low-dose, mid-dose, and high-dose PHEN/TPM-treatment groups, respectively. There were no severely low bicarbonate laboratory results reported in these clinical trials. The applicant employed a restricted fat diet rather than a low carbohydrate diet which may have contributed to events of metabolic acidosis. Patients treated with PHEN/TPM are at greater risk for metabolic acidosis in the presence of renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, and with use of laxatives.

Chronic, untreated metabolic acidosis is associated with an increased risk of nephrolithiasis. Nephrolithiasis events with PHEN/TPM are noted earlier in this review (see EMDAC summary in **Appendix A**). As stated earlier, TPM as a carbonic anhydrase inhibitor promotes nephrolithiasis by reducing urinary citrate excretion and increasing urinary pH (see TPM labeling, WARNING AND PRECAUTIONS section with recommendation to periodically assess serum bicarbonate levels).

3.2.5 CARDIOVASCULAR ADVERSE EVENTS

By way of background for PHEN and CVS risks, Fenfluramine/ Phentermine (FEN/PHEN) was approved over 20 years ago as a weight loss product for short term use. FEN/PHEN is associated with increased risk of cardiac valvulopathy. Fenfluramine and its metabolite (Nor-Fenfluramine) function as a 5HT_{2B} agonist against at the 5HT_{2B} receptor in heart valves. Activation of the 5-HT_{2B} receptor by some valvulopathic drugs is associated with stimulation of destructive fibroblast mitogenesis in cultures of human heart valve interstitial cells. Phentermine is reported to not have significant activity at the 5-HT_{2B} receptor.

Although FEN/PHEN was prescribed for men and women, the majority of its consumers were women many of whom were in their child-bearing years. As early as 1997, FDA reported 24 cases of cardiac valvular disease from Mayo Clinic in women treated with FEN/PHEN for an average of 12 months. FDA received 9 additional cases of valvulopathy associated with off-label use of FEN/PHEN. A Public Health Advisory (July 8, 2007) was issued to over 700,000 HCPs warning them of new valvular heart disease concern with weight loss products indicated for short-term treatment based on reports in women treated for obesity with FEN/PHEN.

The CVS risks reported in PHEN/TPM clinical trials include persistent tachycardia and a decrease in DBP and SBP. One cardiovascular death is reported as cardiorespiratory arrest in a PBO-treated subject. Non-fatal serious cardiac adverse events (SAEs) are reported in 7 PBO-versus 8 PHEN/TPM-treated patients. Ischemic CVS SAEs requiring cardiac catheterization are

reported in 5 patients each, PBO and PHEN/TPM treated. Cerebrovascular ischemic SAEs are reported in 2 PBO-treated patients, 1 each with thalamic infarction and brain stem infarction, respectively, and in 1 high-dose PHEN/TPM-treated patient who experienced acute non-hemorrhagic infarction. A total of 4 PHEN/TPM-treated patients experienced myocardial infarction (MI) compared with none in PBO-treated patients.

Coronary artery disease is reported in 4 PBO- compared with none in PHEN/TPM-treated patients. The cases of ischemic heart events are too few in number to reach any clinically meaningful conclusion about a CVS effect of PHEN/TPM.

Cardiac Disorder Class of AEs are reported in 36 (2.3%) PBO, 4 (1.7%) low-dose, 24 (4.8%) mid-dose, and 78 (4.9%) high-dose PHEN/TPM-treated subjects. The most commonly reported CVS AEs in decreasing order of incidence are palpitations, cardiac arrhythmia, tachycardia and reductions in DBP and SBP. These events are briefly summarized:

- Palpitations: 12 (0.8%), 2 (0.8%), 12 (2.4%), and 27 (2%) in PBO, low-dose, mid-dose and high-dose PHEN/TPM-treated patients, respectively.
- Cardiac arrhythmia-related AEs: 1.8%, 1.3%, 4.2%, and 4.7% in the PBO, low-dose, mid-dose, and high-dose PHEN/TPM-treatment groups, respectively. Patients are twice as likely to experience a cardiac arrhythmia AE with mid- or high-dose PHEN/TPM compared with PBO.
- Tachycardia: 5, 10, 15, and 20 beats above baseline heart rate in PBO, low-dose, mid-dose, and high-dose PHEN/TPM-treated patients, respectively.
- Systolic and diastolic blood pressure: mild to moderate mean reductions in PHEN/TPM-treatment groups compared with the PBO treatment group.

The applicant proposes that TPM has a mitigation effect on the PHEN effect of tachycardia, particularly, with high-dose PHEN/TPM. The clinical significance of PHEN/TPM associated tachycardia and decreases in blood pressure are unknown in these clinical trials.

The CVS effect of QNEXA with chronic use, such as months to years, is unknown. The applicant proposes to conduct a large postmarketing, long term outcome study to assess risks with PHEN/TPM including events of CVS, psychiatric, neurocognitive, and metabolic acidosis in obese adults. The proposed PHEN labeling includes contraindication in patients with advanced arteriosclerosis, cardiovascular disease, or moderate to severe hypertension. Though tachycardia and palpitations are reported events with PHEN, clinical significance of these two events is not characterized in obese patients.

4 APPLICANT'S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY FOR QNEXA

The applicant submitted a proposed REMS with the original NDA (December 28, 2009) and an amended REMS proposal for QNEXA on May 24, 2010 and August 9, 2010) that includes a Medication Guide and communication plan (CP) to address the potential risk for suicidal thoughts and behavior with QNEXA. Each proposed element is described below.

4.1 GOALS

The proposed goals are to:

(b) (4)

4.2 MEDICATION GUIDE

The Medication Guide for QNEXA is dispensed with each QNEXA prescription as part of each unit of use package of QNEXA as bottles of 30 oral capsules (PHEN/TPM dose strengths: low-dose 3.75/23 mg, mid-dose 7.5/46 mg, three-quarter dose 11.25 mg/69 mg, and high-dose 15/92 mg) in compliance with 21 CFR 208.24. The Medication Guide is provided to each patient with each new prescription including refills.

4.3 COMMUNICATION PLAN

The applicant proposes to implement a CP directed to physicians who specialize in treating patients with obesity. The applicant does not clarify physician specialty training, for example, endocrinologists.

The applicant proposes a one to two month delay in availability of QNEXA after approval to provide time to conduct outreach and educate HCPs about the risks associated with QNEXA. The implementation plan and dissemination of CP materials are not clarified by the applicant.

The proposed CP materials are:

- Healthcare provider education on QNEXA risks and appropriate prescribing *
 - On-line QNEXA Training Program* (voluntary) to educate QNEXA prescribers. It includes:
 - Education about appropriate patient selection
 - Product risk and safety information
 - An explanation of the applicant’s restricted “limited” access to QNEXA through designated wholesalers and pharmacies
 - A requirement that prescribers provide identification information to the applicant to support tracking and monitoring prescriber completion of the educational training. *Note: Names and contact information of all physicians who complete the Online QNEXA Training Program are maintained in a secure database managed by the applicant.*
- Dear Healthcare Provider (DHCP) Letter *
- Educational materials accessible via the website www.QNEXA.com or by requesting copies via a toll-free product information line:
 - Medication Guide
 - Patient Support Program Information *
 - Full Prescribing Information
 - Patient/Provider Pregnancy Testing and Contraception Counseling Agreement *
 - Patient Form *

- The Provider/Patient Pregnancy Testing and Contraception Counseling Agreement Form* is provided to prescribers by the applicant. The Agreement Form is signed by the prescriber and patient after the patient is educated by the prescriber on the risks of QNEXA and the need for appropriate contraception. The Agreement Form includes:
 - Specific use of effective contraception by FCBP during QNEXA treatment.
 - Monthly home pregnancy test information.
 - Patients acknowledge that:
 - ✓ I have read and understand the Medication Guide for QNEXA.
 - ✓ My doctor explained the risks and benefits of using QNEXA to me.
 - ✓ I asked my doctor any questions that I had about QNEXA and received answers that I understand.
 - ✓ I am a woman of childbearing potential and will always use effective contraception so that I do not become pregnant. I will take a pregnancy test every month and stop QNEXA immediately if I am pregnant. This is important, since weight loss during pregnancy is not recommended and it is unknown if QNEXA will hurt my unborn baby.
 - ✓ I will alert my doctor if I have any of the following symptoms while taking QNEXA (which will include depression/mood changes, suicidal thoughts, cognitive effects/anxiety, and other symptoms).
 - ✓ I have alerted my physicians to all the medications (prescription and over-the-counter) that I currently take.

The prescriber maintains a copy of the Agreement Form in the patient's medical chart.

The applicant proposes supportive outreach measures to specialized prescribers who treat or manage patients with obesity:

- A letter * reminding prescribers of the On-line Education Training Program and the importance of education in managing patients treated with QNEXA.
- In-person visits via the QNEXA sales force, limited to 150 individuals, to encourage prescribers to participate in the Online Education Training Program.
- Continuing Medical Education * (CME) on obesity for appropriate audiences at conferences and professional meetings.

* These CP materials have not been submitted by the applicant to the Agency for review.

4.4 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

The applicant proposes to submit QNEXA REMS Assessments to FDA at 18 months, 3 years, and 7 years following approval of the QNEXA REMS. The applicant proposes to submit the REMS assessments within 60 days of closure of the assessment intervals as listed above.

4.5 INFORMATION NEEDED FOR ASSESSMENT (REMS ASSESSMENT PLAN)

The applicant proposes the following measures to support assessment of the QNEXA REMS:

- Comparison of prescriber databases for those who have completed on-line education training versus those who have not completed this training.

- Maintain a prescriber database by way of a restricted/limited number of pharmacies to identify prescribers who are treating patients with QNEXA but who have not participated in online education training.
- Periodic surveys on QNEXA prescribing characteristics and dosing patterns based on prescribing data and patient databases (undefined).
- Patient database (undefined).
- Periodically monitor and evaluate wholesaler compliance with the contract agreement for restricted/limited distribution of QNEXA
- Designated pharmacies conduct periodic patient surveys to document patient characteristics and dosing patterns to confirm appropriate dosing.

The applicant has not submitted the instruments and methodologies to support a QNEXA REMS assessment by the Agency.

4.5.1 SURVEYS

The applicant has not submitted a provider and patient survey for review by the Agency.

4.6 SUPPORTIVE MEASURES EXTERNAL TO REMS



Reviewer Comment:

Some of the non-REMS measures described in the applicant's proposal, if required, are consistent with the Food and Drug Administration Amendments Act (FDAAA) ETASU provisions. The advantage for the applicant in doing these voluntary non-REMS measures is the ability to pull back without approval by FDA.

4.7 PROPOSED POSTMARKETING STUDIES

The applicant submits three postmarketing study proposals:

- **Phase 4, Long-Term Cardiovascular Outcomes Study**

The primary objective would be to assess CVS risk with PHEN/TPM in obese adults.

- **QNEXA Pregnancy Exposure Registry**

The primary objective would be to enroll and follow women exposed to QNEXA during pregnancy. The applicant proposes to establish a multi-sponsored Weight Loss Drug Pregnancy Exposure Registry (PER) to enroll women who become pregnant while taking an approved weight loss product or are found to be pregnant within 30 days after discontinuing an approved weight loss product. These data would be compared with data from obese patient pregnancy cohorts not treated with weight loss products.

- **Surveillance Plan**

The primary objective would be to collect and report expedited reports of events of special interest based on risks associated with use of QNEXA.

5 REMS OPTIONS

For purposes of this discussion, we will focus on the possible REMS elements as well as the advantages and limitations of those REMS elements for QNEXA. Based on discussions between DRISK and DMEP and the fact that the AEDs already have an approved Medication Guide to address the risk of suicidality, there is agreement that a QNEXA, with TPM as an active ingredient, will have a Medication Guide.

Among the five key risks associated with QNEXA, DRISK and DMEP concur that the risk of suicidality and the associated teratogenic risk of exposure to TPM based on postmarketing data for TPM monotherapy warrant mitigation under REMS. The CVS, neurocognitive, and metabolic acidosis risks can be adequately managed with product labeling and a postmarketing outcomes study.

5.1 OPTION 1: REMS WITH ONLY A MEDICATION GUIDE

Implementing REMS with only a Medication Guide is a least burdensome REMS option. A Medication Guide would include the same patient information as the FDA ordered class-wide

Medication Guide for AEDs with any additional risks associated with QNEXA as reported in labeling (see **Table 2**).

Table 2.

Overview A Medication Guide includes important serious safety risk(s) to be communicated to and understood by patients. FDA has broadened authority under FDAAA to request labeling changes, pre-approval and post-marketing, that address a specific safety concern(s).	
How could this be accomplished? QNEXA labeling with a Medication Guide is directly affected by the approved labeling for PHEN and TPM. The Medication Guide for TPM serves as a platform for a QNEXA Medication Guide.	
Advantages	Limitations
<ul style="list-style-type: none"> Least burdensome for administrative costs, the healthcare system, and the applicant. 	<ul style="list-style-type: none"> Not likely to be sufficient to manage risk of teratogenic risk of fetal exposure to TPM.

5.2 OPTION 2: REMS WITH A COMMUNICATION PLAN

Implementing REMS with a communication plan, in addition to a Medication Guide, is a second REMS option. A communication plan directed to HCPs includes materials that must be developed and disseminated to prescribers (see **Table 3**).

The risk of suicidality and the associated teratogenic risk with TPM should be understood by prescribers considering pharmacotherapy for obese adult patients in need of weight management. Prescribers should be knowledgeable and prepared to effectively educate all FCBP about risks of increased fertility with weight loss, risk of decreased oral contraceptive effect when used concomitantly with QNEXA, and the importance of pregnancy prevention while taking QNEXA due to associated teratogenic risks with TPM. The FCBP are a large segment predicted to use QNEXA based on PHEN drug usage data for weight management.

The inherent challenge of a REMS communication plan is the limited experience with the effectiveness of education alone to improve safe use of a marketed product. The traditional risk communication materials such as product labeling and DHCP letters are shown to have minimal effect on prescribing behavior or increasing compliance with, for example, a labeled laboratory monitoring recommendation.^{5, 6, 7, 8} Further, pregnancy prevention, in view of consented agreement to use an oral contraception with a barrier method, was not as effective as intended in PHEN/TPM clinical trials resulting in 34 pregnancies.

⁵ Willy M, et al. A Study of Compliance with FDA Recommendations for Pemoline (Cylert). *J Am Acad child Adoles Psychiatry*. 2002 Jul; 41 (7):785-90.

⁶ Graham D, et al. Liver enzyme monitoring in patients treated with troglitazone. *JAMA*. 2001 Aug 15; 286(7):831-3.

⁷ Smalley W, Shatin D, Wysowski D, Gurwitz J, Andrade S, et al. contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action. *JAMA* 2000; 284(23):3036-3039.

⁸ Weatherby LB, Nordstrom BL, Fife D, Walker AM. The Impact of Wording in “Dear Doctor” Letters and in Black Box Labels. *Clin Pharmacol Ther*. 2002; 72:735-742.

A REMS with a communication plan does not address mandates for safe use, such as required pregnancy testing prior to and during therapy if deemed necessary.

Table 3.

<p>Overview A communication plan may include education materials for HCPs about the risks associated with QNEXA and include the importance of HCPs educating patients about the risk of suicidality and the associated teratogenic risk with TPM.</p>	
<p>How could this be accomplished?</p> <ul style="list-style-type: none"> • Education materials may include FDA approved REMS materials as proposed by the applicant. 	
Advantages	Limitations
<ul style="list-style-type: none"> • Educates HCPs about risks with QNEXA. • Only involves development of education materials, implementation steps, and a plan for dissemination of CP materials by the applicant. • Minimal burden to HCPs, healthcare system, and applicant. 	<ul style="list-style-type: none"> • May not be sufficient to manage the risk of teratogenic associated with TPM. • Limited experience with effectiveness of education alone in managing teratogenic risk; not successful in previous programs for highly teratogenic drugs, e.g., isotretinoin.

5.3 OPTION 3: REMS WITH ELEMENTS TO ASSURE SAFE USE

The ETASU can include: 1) mandatory prescriber certification or particular training of HCPs who prescribe QNEXA, 2) mandatory certification of dispensers, such as pharmacies, hospitals, or other health care settings that dispense QNEXA, 3) documentation of safe use conditions such as required negative pregnancy test prior to beginning QNEXA, 4) required HCP counseling of patients about risks with QNEXA, 5) mandatory monitoring of a monthly pregnancy test in FCBP, and/or 6) that patients receiving QNEXA be enrolled in a registry. REMS can include one or more element that may or may not link to a restricted distribution plan (see **Tables 4 - 6**). Each element is presented below with its advantages and limitations..

5.3.1 PRESCRIBER CERTIFICATION

Table 4.

<p>Overview Prescriber certification includes acknowledgement that prescribers: 1) understand the risk of suicidality and the associated teratogenic risk with TPM, 2) can diagnose and treat SAEs reported with QNEXA, and 3) will report SAEs under the REMS program.</p>
<p>How could this be accomplished?</p> <ul style="list-style-type: none"> • Prescribers review FDA approved REMS education materials as described above in Table 3. • Prescribers sign a form acknowledging their understanding of the risks with QNEXA prior to prescribing it and agree to pregnancy testing requirements, closely monitoring of patients for SAEs, etc. <ul style="list-style-type: none"> ○ If applicable for QNEXA, prescribers agree to monitor patients by way of a screening instrument, for example, the Patient Health Questionnaire (PHQ-9), to help select and monitor for depression, and, for example, a laboratory test result

such as a monthly (-) pregnancy test to monitor for a fetal exposure to QNEXA.	
Advantages	Limitations
<ul style="list-style-type: none"> • Employing mandatory prescriber certification in REMS supports all HCPs having similar baseline knowledge of the risks associated with use of QNEXA. • Mandates prescriber acknowledgement of understanding risks, requirements for safe use of QNEXA, and reporting SAEs. • If this ETASU is implemented without other ETASU, there is no affect on product distribution. • Supports survey assessment of prescriber knowledge of risks with QNEXA including appropriate monitoring (if applicable, under an ETASU), documentation of safe-use conditions. 	<ul style="list-style-type: none"> • Adds burden for prescribers and applicant. • Lacks patient-level documentation of compliance with safe use conditions. • Experience with isotretinoin SMART Program indicates that attestation of requirements did to always result in compliance with safe use conditions. • Requires additional ETASU to support compliance of prescribers and documentation of safe use conditions, e.g., lab test result.

5.3.2 CERTIFICATION OF DISPENSER

Table 5.

Overview
<p>The certification of dispensers, e.g., pharmacies, practitioners, and or healthcare settings, requires acknowledgement by a responsible person who understands the risks with QNEXA and who agrees to develop and implement appropriate polices and procedures to ensure that QNEXA is dispensed from a certified prescriber’s prescription or</p> <p>confirmation of a mandated safe use condition e.g., a laboratory test, e.g., monthly (-) pregnancy test prior to dispensing if that element is also employed (see Section 5.3.3 below).</p> <p>A certified dispenser would be responsible for education of their staff about risks with QNEXA.</p> <ul style="list-style-type: none"> • Periodic recertification and re-enrollment of a dispenser may be required. <p>How could this be accomplished?</p> <ul style="list-style-type: none"> • Dispenser reviews FDA approved REMS education materials, e.g., education slide deck, brochure, HCP Fact Sheet, web-based course and/or other written materials. • Dispenser attests to having appropriate polices and procedures as follows: <ul style="list-style-type: none"> ○ Educate staff about risks with QNEXA and require HCP to verify a monthly (-) pregnancy prior to dispensing QNEXA. ○ Capable of verifying prescriber certification. ○ Processes prescriptions only from certified prescribers (written or electronic). ○ Verifies patient’s monthly (-) pregnancy test result prior to filling a QNEXA prescription written by a certified prescriber (if applicable) ○ Capable of tracking non-compliant prescribers and reporting them to applicant. • Manufacturers, wholesale distributors, specialty distributors only ship QNEXA to a certified dispenser.

Advantages	Limitations
<ul style="list-style-type: none"> • Ensures that QNEXA is only dispensed if controlled: <ul style="list-style-type: none"> ○ Prescription is written by a certified prescribers. ○ Dispensed by a certified dispenser. • Supports safe use condition documentation, e.g., monitoring (-) pregnancy test prior to dispensing QNEXA (if documentation of safe use element is employed). 	<ul style="list-style-type: none"> • Burdensome to all stakeholders so this would likely shift use to approved PHEN and TPM formulations that are available by prescription without ETASU. • Only likely successful if documentation of safe use conditions and patient registry required to track outcomes.

The applicant only ships QNEXA to a certified dispenser, linking drug distribution and HCP monitoring a safe use condition, e.g., monthly (-) pregnancy test result. Unless QNEXA treated patients are enrolled in a patient registry, documentation of a monitored laboratory test result would not be required as an additional ETASU because there is no pathway to track these data. Therefore, certification of dispensers is more effective and efficient if certification of prescribers is a concurrently required ETASU under REMS.

5.3.3 DOCUMENTATION OF SAFE USE CONDITIONS / PATIENT ENROLLMENT/ PATIENT MONITORING

Table 6.

Overview	
<p>According to FDAAA, documentation of evidence or other documentation of safe use conditions, patient enrollment and patient monitoring, each, constitutes a separate ETASU. There is actually a significant amount of overlap in these elements. The tools/instruments may include requiring laboratory monitoring prior to dispensing a drug, the patient signing a “Patient Acknowledgement Form” documenting that they understand the risks and benefits of QNEXA, and/or that patients are monitored on a routine basis while receiving and/or following discontinuation of the drug.</p>	
How could this be accomplished?	
<ul style="list-style-type: none"> • Prescribers enroll in a REMS program. • Prescriber may determine if a patient has adequately tried and failed diets, exercise programs, fulfills weight criteria for QNEXA and, therefore, is a candidate for pharmacotherapy of obesity. • Prescriber documents patient counseling for men and women about QNEXA risks of suicidality, associated teratogenic risk with QNEXA for FCBP, importance of pregnancy prevention, and choosing appropriate contraception for a FCBP. A patient registry for FCBP may or may not include a contraception requirement (FDA understands that pregnancy tests, alone, do not prevent a pregnancy). • Prescriber verifies initial (-) pregnancy test in a FCBP. • Prescriber enrolls all patients in a QNEXA patient registry; patient and prescriber sign the patient acknowledgement form. • Prescriber sends signed patient enrollment form and documentation of (-) pregnancy test result in FCBP to applicant (or designed vendor). • Pharmacy verifies authorization based on (-) pregnancy test result in FCBP before dispensing QNEXA. 	
Advantages	Limitations

<ul style="list-style-type: none"> • Active risk mitigation steps, e.g., monthly (-) pregnancy test in FCBP, verified by prescriber, regular monitoring for depression (PHQ-9 screening) leading to suicidality. • Supports adherence with QNEXA labeling including Contraindications, e.g., pregnancy category X. • Increases REMS assessment capabilities: <ul style="list-style-type: none"> ○ Captures all patients treated QNEXA. ○ Monitors SAEs. ○ Better capture of outcomes than relying on spontaneous reporting. ○ Tracks prescriber adherence to REMS program. 	<ul style="list-style-type: none"> • Still relies on compliance by patients with pregnancy prevention strategies, e.g., compliance with contraceptive measures. • High burden to prescribers, patients, health care system, and applicant. <ul style="list-style-type: none"> ○ Requires prescriber and dispenser certification, patient registry, and FCBP monthly laboratory testing. ○ Affects drug distribution. ○ Pharmacies need authorization # from applicant or contracted vendor to dispense QNEXA. ○ May reduce patient access to QNEXA.
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6 DISCUSSION

There are five risks that we considered in determining whether routine risk mitigation is appropriate for QNEXA or whether additional mitigation strategies are warranted. The risks include CVS effects, psychiatric effects including suicidality, neurocognitive effects, metabolic acidosis, and teratogenicity with TPM.

We do not believe REMS is required to ensure benefits outweigh risks for neurocognitive effects and metabolic acidosis as these risks did not appear to warrant more than routine labeling and postmarketing pharmacovigilance. With regard to CVS effects, weight loss products have a history of associated CVS effects, e.g., sibutramine (MERIDA). As stated in this review, FEN/PHEN was withdrawn from the market due to associated valvulopathy. Obesity is well known to be associated with CVS co-morbidities. Based on the 12-month clinical safety data, it is not possible to attribute CVS event causality to PHEN/TPM alone versus the underlying condition of obesity in the PHEN/TPM clinical development program. Furthermore, the CVS events possibly associated with QNEXA may not be amenable to REMS monitoring strategy since these events are too small in number to identify the at-risk population and/or monitor by an enrollment criteria to prevent CVS events. Therefore, we believe the CVS risk should be further characterized through a post-marketing study as proposed by the applicant.

We do believe that REMS is required for QNEXA to ensure the benefits outweigh the risks of suicidality and teratogenicity.

TPM and Risk of Suicidality with QNEXA

Though no completed suicides are reported in PHEN/TPM clinical trials, the EMDAC cautioned FDA that we may see an increase risk of depression leading to suicidality with real-world use of QNEXA. By example, FDA required a large outcome study with rimonabant (over 10,000 patients) to better characterize the safety risks. The applicant for QNEXA plans to submit two-year clinical trial safety data to FDA to better characterize risks with QNEXA and proposes to conduct a postmarketing observational outcome study.

Furthermore, based on final results of an FDA analysis of suicidality, defined as suicidal behavior and ideation, in clinical trials of AEDs, FDA concluded that the class of AEDs increases the risk

of suicidality. To address this increased risk of suicidality, FDA notified all manufacturers of AEDs that warnings to this effect are necessary in the prescribing information and that REMS that includes a Medication Guide was necessary for AED products to ensure the benefits outweigh the risks. TPM is an AED and active ingredient in QNEXA. In the absence of evidence that the risk of suicide is augmented with QNEXA beyond the AED Class risk, the QNEXA REMS should include a Medication Guide to maintain consistency with TPM monotherapy.

There is concern that TPM is associated with teratogenic risk. While the applicant reports a RR of 1.09 for major malformations with TPM monotherapy in epilepsy compared to controls, other data suggest that TPM is a probable human teratogen, albeit the risk for teratogenicity does not appear to be as high as what is observed with isotretinoin or thalidomide. The North American AED Pregnancy Registry reports a RR of teratogenicity with TPM as 2.8 compared to controls. The types of malformations observed in this registry, animal data, and postmarketing reports include cleft lip, craniofacial malformations, skeletal limb malformations, and cardiovascular malformations. The risk of teratogenicity with QNEXA is unclear. Based on three non-clinical reproductive toxicity studies, TPM monotherapy is associated with harmful effects. However, among 34 pregnancies in PHEN/TPM clinical trials, 19 delivered infants without major malformations, 6 ended in elective terminations, 6 ended in spontaneous terminations, 1 each as an ectopic pregnancy, unknown outcome, and lost to follow-up. Furthermore, the dose of TPM in proposed doses of QNEXA is less than the recommended dose for topiramate formulations marketed for epilepsy and migraine.

Although the risk of teratogenicity with QNEXA is not fully understood, we believe that a REMS should be required to ensure the benefits outweigh these risks based upon what we know about the associated risk of teratogenicity with TPM.

REMS are intended to meet specific risk mitigation goals for a product that requires strategies beyond product labeling to ensure safe use in the post-marketing setting. At this time, in considering the most appropriate REMS for QNEXA, if approved, a number of important factors must be carefully weighed in the context of REMS:

- Current PHEN usage for weight loss is approximately (b) (4) prescriptions per year. Further more, there are 34 pregnancies in Phase 3 clinical trials with PHEN/TPM, a controlled setting where it was likely that the risks of teratogenicity were clearly presented to enrolled and consented clinical trials patients.
- PHEN and TPM, the two active ingredients in QNEXA, are available by prescription as generic products. If QNEXA is approved with a REMS with ETASU, prescribing will likely shift from a drug with a restricted access program to the more accessible components of the combination product. We must recognize this potential dynamic of more easily available weight loss products without REMS as we consider how to address the teratogenic risk of fetal exposure to TPM for mitigation under a QNEXA REMS.
- TPM and obesity, itself, may reduce the efficacy of oral contraceptives. Lower TPM doses are reported to be less likely to have effect on efficacy of oral contraceptives compared with higher TPM doses in patients with epilepsy. Since use of oral contraception is an important mitigation strategy and is one of the tools used in many of the currently approved REMS for products with teratogenicity, there will need to be a thoughtful discussion of what the “effective contraception” recommendations should be for this population taking PHEN/TPM as part of the overall mitigation strategy for QNEXA.

- QNEXA is among the first weight loss formulations proposed for chronic use. While chronic is not defined in PHEN/TPM clinical development program for obesity or by FDA, the REMS for QNEXA would need to consider in the chronicity of use and the burden of employing risk mitigation strategies such as monthly pregnancy testing for this proposed, chronic use indication.

7 CONCLUSION AND RECOMMENDATIONS

Considering all these factors discussed above, restricted distribution/ETASU for QNEXA cannot be ruled-out based on practical factors such as predicted widespread drug usage in females of childbearing potential. A decision should be based on risks associated with use of QNEXA. However, this decision cannot be made outside the context of burden and feasibility relative to component products availability. Therefore, we recommend a fuller discussion of the risk of teratogenicity with PHEN/TPM as well as the elements that would be required in the QNEXA REMS at a Center Director Briefing and, possibly, at a future advisory committee meeting specific for REMS with QNEXA.

A pharmacodynamic study should be required to better characterize the effect of concomitant QNEXA and oral contraceptive use in obese women.

There remain many outstanding concerns, questions, and clarifications in amended REMS for QNEXA submissions from the applicant (submitted August 9, 2010).

8 APPENDICES

Summary of the EMDAC on July 15, 2010

The committee expressed distress that 34 pregnancies (1% pregnancy rate) occurred in the clinical trials in patients who acknowledged using oral contraceptives with a barrier method under Informed Consent. Nineteen of 34 pregnancies delivered normal term infants. The committee expressed concern and uncertainty about teratogenic risks with TPM and emphasized that obesity, alone, is associated with adverse pregnancy outcomes. Though the absolute risk with TPM appears small and can probably be managed with counseling, the committee cautioned that FDA does not know how QNEXA will be marketed, if approved, in the real-world. The committee strongly urged FDA to include pregnancy category X in QNEXA labeling. The committee confirmed with the Maternal Health Team representative at the EMDAC that PHEN is not without associated teratogenic risk though these data are limited.

One committee member recommended that FDA review all clinical safety data from the three proposed weight loss applications (LORQESS, CONTRAVE, and QNEXA) before issuing a recommendation for QNEXA.

The committee raised concern if REMS actually affects patients' behavior and judgment. The committee recommended that FDA consider how to appropriately counsel patients about the risks associated with QNEXA. Though ETASU were minimally mentioned, committee members recommended patient/provider registry with the same caveats discussed above. There was no mention of a restricted distribution program for access to QNEXA.

The committee concurred that Phase 3 clinical trials won on the co-primary efficacy variables, percent of weight loss and percentage of subjects with at least 5% weight loss compared to placebo (PBO) at Week 28 (Study OB-301) and Week 56 (Study OB-302 and OB-303) for PHEN/ TPM. The committee expressed concern about lack of efficacy data for non-responders and the need to identify non-responders as early due to the plateau effect of PHEN/TPM at 4 to 6

months and risks with QNEXA. The committee concurred that PHEN/TPM is more efficacious for weight loss than PHEN or TPM monotherapy, alone.

In regard to safety, the committee expressed significant concern about five key risks: psychiatric, neurocognitive, cardiovascular (CVS), metabolic acidosis, and associated teratogenic risk with fetal exposure to TPM. The committee strongly urged longer-term safety data through at least 24 months exposure to better characterize the safety profile of PHEN/TPM.

The committee conveyed strong concern about psychiatric AEs as a cause for discontinuations in PHEN/TPM clinical trials with 26% discontinuations across all PHEN/TPM-treated subjects compared with 12% PBO-treated patients. The committee expressed concern about early onset of psychiatric AEs within three months of starting PHEN/TPM treatment. Discontinuations are approximately double with high-dose PHEN/TPM-treated compared with PBO-treated patients; depression appears to drive drop-outs. Psychiatric AEs occurred in 21% high-dose PHEN/TPM-treated patients compared with 10% PBO-treated patients. The committee voiced significant concern about dose-related increases in psychiatric AEs including sleep disorders, anxiety disorders, and depression with high-dose PHEN/TPM.

Neurocognitive AEs (attention, memory impairment, and language difficulty demonstrate a dose-related increase with PHEN/TPM, in particular, high-dose PHEN/TPM.

In regard to CVS events, the committee expressed concern about: 1) a dose-related increase in heart rate, 2) a dose-related decrease in diastolic and systolic blood pressure (DBP, SBP) compared with PBO, and 3) syncope with high-dose PHEN/TPM. One death reported as cardiorespiratory arrest was experienced in a PBO-treated patient. The committee focused on serious CVS events of non-fatal MI: 4 PHEN/TPM-treated patients compared with none in PBO-treated patients, and emergency revascularization procedures: 4 PBO-treated patients, 3 patients required stent placement and one required coronary artery by-pass graft.

Committee concerns about metabolic acidosis include:

- 1) failure of laboratory monitoring to include free fatty acids,
- 2) lack of data about diet plans or exercise programs employed in these clinical trials
- 3) increased incidence of nephrolithiasis including 2 SAEs: nephrolithiasis is reported in 20 patients (1.3%) with high-dose PHEN/TPM compared with 5 patients (0.3%) with PBO-treatment,
- 4) large proportion (30%) of high-dose PHEN/TPM-treated patients with serum bicarbonate levels < 21 mEq/ L,
- 5) unknown long-term effects PHEN/TPM on bone stability, fracture risks, and bone growth.

The committee expressed significant concern about differing opinions among the applicant, the Agency, AERS data, and the North American AED Pregnancy Registry data, in regard to malformations associated with TPM monotherapy. The applicant reports a relative risk (RR) for major malformation associated with TPM monotherapy in epilepsy as 1.09 (95% CI 0.58 to 2.06) compared with controls. However, the North American AED Pregnancy Registry reports prevalence of major malformations as 3.8% (11 events among 289 pregnancies) and RR for major malformations associated with TPM as 2.8 (95% CI: 1.0 to 8.1) compared with controls.

Major malformations causally associated with TPM monotherapy are exposed cleft lip, isolated cleft lip, and skeletal limb malformations compared with the expected prevalence in the general population. None of these data was reassuring to the EMDAC about the associated teratogenic risks with TPM (see Section 3.2.1 Teratogenicity, in this review).

Labeling recommendations are:

- 1) Include caution about risks of working with machinery and driving a vehicle.
- 2) Include Contraindication of QNEXA in patients with a history of nephrolithiasis.
- 3) Include Contraindication of QNEXA in pregnancy; include pregnancy category X.
- 4) Develop a Medication Guide with easily understandable information about pregnancy prevention and contraception including risk of decreased effect of oral contraceptives with QNEXA; risk of weight loss increasing fertility; and importance of a patient immediately telling her treating doctor if she experiences changes in menses suggesting pregnancy so that QNEXA can be discontinued.
- 5) Include precaution to avoid use of laxatives with QNEXA due to risk of metabolic acidosis.
- 6) Exclude high-dose QNEXA due to dose-related risks in 12-month clinical safety data.

Additional recommendations include:

- 1) Plan to analyze TPM data for depression as PHEN/TPM appears to increase mild to moderate depression in exposed subjects.
- 2) Require long-term CVS outcome study and consider how to screen enrollment of obese subjects with coronary artery disease as well as risk for suicidal ideation; include laboratory parameters for thyroid function and vitamin D levels prior to PHEN/TPM exposure because weight loss is associated with subclinical hypothyroidism. Obesity is associated with low vitamin D levels.
- 3) Employ creatinine cut-off similar to clinical guidelines for Metformin to support appropriate QNEXA prescribing.
- 4) Employ caution with a pediatric indication for weight loss based on risk of chronic metabolic acidosis with TPM reported as more problematic in children (leading to rickets and decreased bone growth) than in adults.
- 5) Require fracture data, bone density testing, and serum bicarbonate levels in PHEN/TPM clinical trials and larger study of obese women treated with PHEN/TPM.
- 6) Monitor for inevitable dose-creep and increased risk of psychoses and neurocognitive events with high-dose QNEXA.
- 7) Require monitoring of QNEXA pregnancy outcomes, separate from the North American AED Pregnancy Registry, and consider a pregnancy prevention program for QNEXA.

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/s/

CAROLYN L YANCEY

10/11/2010

QNEXA (phentermine/topiramate) REMS Options Final Review

CLAUDIA B KARWOSKI

10/12/2010

concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

NDA/BLA #s: 22580
Products: QNEXA (phentermine/topiramate) Capsules 3.75mg/23 mg, 7.5 mg/46 mg, 15 mg/92mg
APPLICANT: Vivus, Inc.
FROM: Eric Colman, M.D.
DATE: September 23, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for QNEXA (phentermine/topiramate) to ensure that the benefits of the drug outweigh the risks of suicidal thoughts or behaviors. In addition, depending on the outcome of the comprehensive assessment of the teratogenic potential of phentermine/topiramate, the REMS may also need to address the potential risk for teratogenicity or fetal harm. In reaching the determination that a REMS is necessary, we considered the following:

- A. Approximately two out of three adults in the United States are considered overweight (BMI 25 to 29.9 kg/m²) or obese (≥ 30 kg/m²). This estimate is based on the 2007-2008 National Health and Nutrition Examination Survey database published in the Journal of American Medical Association in January 2010. Phentermine, a component of QNEXA (phentermine/topiramate), is approved for short-term weight loss and is the most widely prescribed weight loss drug with approximately (b) (4) (b) (4) prescriptions dispensed in outpatient retail pharmacy settings in 2009.

- B. Obesity is associated with numerous co-morbidities, including dyslipidemia, coronary artery disease, hypertension, stroke, and type 2 diabetes mellitus. The second leading modifiable risk factor for death in the United States is overweight.
- C. The benefit of QNEXA (phentermine/topiramate) is expected based on significant weight loss over lifestyle modification and modest improvements in weight-related co-morbidities. The effect of pharmacological weight-loss on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.
- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the most serious risks suicidal thoughts or behaviors, phentermine/topiramate has been associated with teratogenicity, fetal harm, cognitive-related dysfunction, metabolic acidosis, nephrolithiasis, and acute myopia associated with secondary angle closure glaucoma.
- F. QNEXA (phentermine/topiramate) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for QNEXA (phentermine/topiramate). FDA has determined that QNEXA (phentermine/topiramate) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of QNEXA (phentermine/topiramate). FDA has determined that QNEXA (phentermine/topiramate) is a product for which patient labeling could help prevent serious adverse effects. FDA has determined that QNEXA (phentermine/topiramate) has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use QNEXA (phentermine/topiramate).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

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/s/

AMY G EGAN
10/27/2010

ERIC C COLMAN
10/27/2010