

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22580Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 022580	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Qsymia		
Established/Proper Name: phentermine and topiramate extended-release, CIV		
Dosage Form: capsule		
Strengths: 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, 15/92 mg		
Applicant: Vivus, Inc.		
Date of Receipt: October 17, 2011		
PDUFA Goal Date: July 17, 2012		Action Goal Date (if different):
Proposed Indication(s): An adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: <ul style="list-style-type: none">• 30 kg/m² or greater (obese) (1) or• 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia (1)		
<u>Limitations of Use:</u> <ul style="list-style-type: none">• The effect of Qsymia on cardiovascular morbidity and mortality has not been established (1). The safety and effectiveness of Qsymia in combination with other products intended for weight loss, including prescription and over-the-counter drugs, and herbal preparations, have not been established (1).		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Topamax (topiramate) NDA 20505 (100 mg, 200 mg, 50 mg oral tablets)	FDA's general findings of safety and efficacy
Topamax (topiramate) NDA 20844 (15 mg, 25 mg oral capsules)	FDA's general findings of safety and efficacy
Topamax Product Monograph 2007	FDA's general findings of safety and efficacy
Ionamin (phentermine resin) NDA 11613	FDA's general findings of safety and efficacy

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s).

a) Topamax® (topiramate) NDA 20-505 (100 mg, 200 mg, 25mg, 50 mg oral tablets)

The scientific bridge from QNEXA to Topamax® NDA 20-505 was attained by VIVUS Clinical Study OB-110, as submitted in the original NDA. Clinical Study OB-110 was a randomized, open-label, single-dose, parallel-design study which compared QNEXA Capsule (PHEN/TPM 15/92 mg) to 100 mg topiramate tablet (Topamax). Study OB-110 showed (Table 1 and Figure 1) that the mean topiramate C_{max} and AUC following one QNEXA 15/92 capsule was not higher than those following a 100 mg Topamax tablet.

b) Topamax® (topiramate) NDA 20844 (15 mg, 25 mg oral capsules)

The Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2009 prescribing information for Topamax lists both tablets and capsules as available dosage forms. Although Section 14 of the prescribing information (Clinical Studies) does not specify which dosage form was used, Section 12.3 (Pharmacokinetics) states "The sprinkle formulation is bioequivalent to the immediate release tablet formulation and, therefore, may be substituted as a therapeutic equivalent."

Thus the scientific bridge from QNEXA to the Topamax NDA 20-844 (capsules) is through the above mentioned Topamax NDA 20-505 (for tablets) that were used in VIVUS Study OB-110.

c) Topamax® Product Monograph, 2007

Drug monographs are an alternate way of presenting the contents of FDA-approved labeling. The Topamax Product Monograph from 2007 was referenced for completeness in evoking Section 505(b)(2) for the QNEXA NDA. The scientific bridge would be the prescribing information approved for the above mentioned NDAs for Topamax.

d) Adipex-P® (phentermine) ANDA 85-128 (37.5 mg oral tablet)

The scientific bridge from QNEXA to Adipex-P® ANDA 85-128 was attained by VIVUS Clinical Study OB-110, as submitted in the original NDA. OB-110 was a randomized, open-label, single-dose, parallel-design study which compared QNEXA Capsule (PHEN/TPM 15/92 mg) to 37.5 mg phentermine tablet (Adipex-P). Study OB-110 showed (Table 2 and Figure 2) that the mean phentermine Cmax and AUC following one QNEXA 15/92 capsule was not higher than those following a 37.5 mg Adipex tablet.

e) Adipex-P® (phentermine) ANDA 88-023 (37.5 mg oral capsule)

The Gate Pharmaceuticals (Teva) 2005 prescribing information for Adipex® lists both tablets and capsules as available and equivalent dosage forms. Thus the scientific bridge from QNEXA to Adipex® ANDA 88-023 (for capsules) is through the above mentioned Adipex® ANDA 85-128 (for tablets) that were used in VIVUS Study OB-110.

f) Ionamin (phentermine resin) NDA 11-613

ANDA 85-128 for Adipex® was submitted pursuant to Section 505(j) of the FD&C Act.

The Approval Package for the ANDA 85-128 includes a memorandum in which FDA's Division of Regulatory Affairs contended that phentermine resin and phentermine hydrochloride were interchangeable based on a review of a bioequivalence study by the FDA's Division of Biopharmaceutics.

Thus the scientific bridge to the Ionamin NDA 11-613 is attained by reference to the content of the Adipex ANDA 85-128. VIVUS believes this body of information demonstrates the relationship of the referenced products and proposed product in support of our 505(b)(2) NDA submission.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES X NO ☐

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product? N/A

YES X NO ☐

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

Please see response to Question #6.

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES X NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES X NO ☐

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Topamax (topiramate)	NDA 20505 (100 mg, 200 mg, 50 mg oral tablets) NDA 20844 (15 mg, 25 mg oral capsules)	Y
Ionamin (phentermine resin)	NDA 11613	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A X YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES NO X

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES X NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process: Ionamin (phentermine resin)

c) Described in a monograph?

YES NO X
If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES X NO
If "YES", please list which drug(s) and answer question d) i. below.
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Ionamin (phentermine resin)

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO X

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication (obesity) and a new formulation (combination product/extended release).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

*If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? N/A

YES ☐ NO ☐

Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

☐ NO

YES

If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☐ NO ☒

If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): None

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): all for Topamax:

U.S. Patent No. 5,998,380
U.S. Patent No. 6,503,884
U.S. Patent No. 7,018,983
U.S. Patent No. 7,125,560
U.S. Patent No. 7,498,311

No patents are listed for phentermine.

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES X NO ☐

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 5,608,075

- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- X 21 CFR 314.50(i)(1)(ii): No relevant patents. [for phentermine]

- X 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number	Method of Use/Code
U.S. Patent No. 5,998,380	U-598
U.S. Patent No. 6,503,884	U-598
U.S. Patent No. 7,018,983	U-723
U.S. Patent No. 7,125,560	U-766
U.S. Patent No. 7,498,311	U-955

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

POOJA DHARIA
07/17/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	22580
Product Name:	Qsymia (phentermine/topiramate extended release) capsules
PMR/PMC Description:	<p>A clinical pharmacology trial under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic and pharmacodynamic parameters related to Qsymia doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg in pediatric patients ages 12 to 17 (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population. This study may not be initiated until (b) (4)</p> <p>the results of the juvenile animal study PMR have been submitted and reviewed.</p>

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/30/2015
	Study/Trial Completion:	11/30/2015
	Final Report Submission:	05/31/2016
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Qsymia is ready for approval for use in adults. However, pediatric studies have not been completed.

Qsymia has been associated with an elevation in heart rate (1 to 2 bpm) in obese adults regardless of weight loss. At this time, there is insufficient evidence to conclusively quantify the long-term cardiovascular morbidity and mortality associated with Qsymia use. Therefore, the applicant will be required to conduct a post-approval cardiovascular outcomes trial in adults. Pediatric studies in this age group should not be initiated until an interim analysis of major adverse cardiovascular events from the cardiovascular trial in adults has been submitted to the Agency and found to exclude evidence of increased harm, and the results of the juvenile animal study PMR have been submitted and reviewed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to establish the pharmacokinetics and pharmacodynamics of Qsymia in the pediatric subpopulation to determine appropriate dosing in this age group for the safety and efficacy study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical pharmacology study under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic and pharmacodynamic parameters related to Qsymia doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg in pediatric patients ages 12 to 17 (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population. This study may not be initiated until an interim analysis of major adverse cardiovascular events from the cardiovascular outcome trial in adults has been submitted to the Agency and found to exclude evidence of increased harm, and the results of the juvenile animal study PMR have been submitted and reviewed.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Subpopulation: Pediatric patients ages 12-17 (inclusive) with obesity with/without co-morbidities
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	22580								
Product Name:	Qsymia (phentermine/topiramate extended release) capsules								
PMR/PMC Description:	<p>A 52-week randomized, double-blind, placebo-controlled pediatric study under the Pediatric Research Equity Act (PREA) to evaluate the safety and efficacy of Qsymia for the treatment of obesity in pediatric patients ages 12 to 17 years (inclusive). This study may not be initiated until (b) (4)</p> <p>the results of the juvenile animal study PMR have been submitted and reviewed.</p>								
PMR/PMC Schedule Milestones:	<table><tr><td>Final Protocol Submission:</td><td>11/30/2016</td></tr><tr><td>Study/Trial Completion:</td><td>03/31/2018</td></tr><tr><td>Final Report Submission:</td><td>09/30/2018</td></tr><tr><td>Other:</td><td></td></tr></table>	Final Protocol Submission:	11/30/2016	Study/Trial Completion:	03/31/2018	Final Report Submission:	09/30/2018	Other:	
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Other:									

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Qsymia is ready for approval for use in adults. However, pediatric studies have not been completed.

Qsymia has been associated with an elevation in heart rate (1 to 2 bpm) in obese adults regardless of weight loss. At this time, there is insufficient evidence to conclusively quantify the long-term cardiovascular morbidity and mortality associated with Qsymia use. Therefore, the applicant will be required to conduct a post-approval cardiovascular outcomes trial in adults. Studies in this age group should not be initiated until an interim analysis of major adverse cardiovascular events from the cardiovascular trial in adults has been submitted to the Agency and found to exclude evidence of increased harm, and the results of the juvenile animal study PMR have been submitted and reviewed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to establish the safety and efficacy of Qsymia in the pediatric subpopulation after 1 year of treatment

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 52-week randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of Qsymia in adolescents, ages 12 – 17 years (inclusive) (b) (4)

(b) (4)

This study may not be initiated until an interim analysis of major adverse cardiovascular events from the cardiovascular outcome trial in adults has been submitted to the Agency and found to exclude evidence of increased harm, and the results of the juvenile animal study PMR have been submitted and reviewed. (b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☒ Other (provide explanation)

Subpopulation: Pediatric patients 12-17 (inclusive) with obesity with/without co-morbidities

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?

- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	22580
Product Name:	Qsymia (phentermine/topiramate extended release) capsules
PMR/PMC Description:	A clinical pharmacology study under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic and pharmacodynamic parameters related to Qsymia doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg in pediatric patients ages 7 to 11 (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population. This study may not be initiated until the results of the adolescent Qsymia safety and efficacy study have been submitted and reviewed by the Agency.
PMR/PMC Schedule Milestones:	Final Protocol Submission: 03/30/2019
	Study/Trial Completion: 06/30/2019
	Final Report Submission: 12/31/2019
	Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Qsymia is ready for approval for use in adults. However, pediatric studies have not been completed.

Qsymia has been associated with an elevation in heart rate (1 to 2 bpm) in obese adults regardless of weight loss. At this time, there is insufficient evidence to conclusively quantify the long-term cardiovascular morbidity and mortality associated with Qsymia use. Therefore, the applicant will be required to conduct a post-approval cardiovascular outcomes trial in adults. Pediatric studies in this age group should not be initiated until the results of the adolescent Qsymia safety and efficacy study have been submitted and reviewed by the Agency

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to establish the pharmacokinetics and pharmacodynamics of Qsymia in the pediatric subpopulation to determine appropriate dosing in this age group for the safety and efficacy study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical pharmacology study under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic and pharmacodynamic parameters related to Qsymia doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg in pediatric patients ages 7 to 11 (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population. This study may not be initiated until the results of the adolescent Qsymia safety and efficacy study have been submitted and reviewed by the Agency.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Subpopulation: Pediatric patients ages 7-11 (inclusive) with obesity with co-morbidities
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	22580
Product Name:	Qsymia (phentermine/topiramate extended release) capsules
PMR/PMC Description:	A 52-week randomized, double-blind, placebo-controlled pediatric study under the Pediatric Research Equity Act (PREA) to evaluate the safety and efficacy of Qsymia for the treatment of obesity in pediatric patients ages 7 to 11 (inclusive). This study may not be initiated until results from the Qsymia adolescent safety and efficacy study have been submitted and reviewed by the Agency.
PMR/PMC Schedule Milestones:	Final Protocol Submission: 06/30/2019
	Study/Trial Completion: 10/31/2021
	Final Report Submission: 04/30/2022
	Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Qsymia is ready for approval for use in adults. However, pediatric studies have not been completed.

Qsymia has been associated with an elevation in heart rate (1 to 2 bpm) in obese adults regardless of weight loss. At this time, there is insufficient evidence to conclusively quantify the long-term cardiovascular morbidity and mortality associated with Qsymia use. Therefore, the applicant will be required to conduct a post-approval cardiovascular outcomes trial in adults. Studies in this age group should not be initiated until results from the Qsymia adolescent safety and efficacy study have been submitted and reviewed by the Agency.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to establish the safety and efficacy of Qsymia in the pediatric subpopulation after 1-year of treatment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 52-week randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of Qsymia in children, ages 7 - 11 years (inclusive) (b) (4)

This study may not be initiated until results from the Qsymia adolescent safety and efficacy study have been submitted and reviewed by the Agency.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)

Subpopulation: Pediatric patients ages 7-11 (inclusive) with obesity with co-morbidities

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	22580
Product Name:	Qsymia (phentermine/topiramate extended release) capsules
PMR/PMC Description:	A juvenile animal study with phentermine and topiramate coadministration to assess behavior, learning and memory, (b) (4) and ocular toxicity, and general nervous system and bone/teeth development, including assessments of drug exposure and reversibility of any observed toxicity.
PMR/PMC Schedule Milestones:	Final Protocol Submission: 04/30/2013
	Study/Trial Completion: 02/28/2014
	Final Report Submission: 12/31/2014
	Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The proposed indication excludes pediatric use. Pediatric clinical trials are expected as part of a pediatric plan, including deferral for adolescents (aged 12-17) and pre-adolescents (aged 7-11) with waiver for young children (aged 0-6). Bone, teeth, brain and nervous system development continue throughout childhood and adolescence whereas toxicity in adults may differ. Clinical trials have evaluated the safety of the proposed drug combination in adults but safety assessment in children has not been assessed. Juvenile animal studies with phentermine and topiramate coadministration should be conducted prior to pediatric clinical trials to investigate effects on behavior, learning and memory, (b) (4) and ocular toxicity, and general nervous system and bone/teeth development.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Topiramate has been studied in juvenile animals but neither phentermine nor combined phentermine and topiramate have been assessed in juvenile animals post-weaning. Phentermine and topiramate are active in the central nervous system and cause neurological adverse events in some patients. Topiramate affects bone mineral density and growth plate density in juvenile animals and phentermine causes teeth toxicity in adult animals. Bone, teeth, brain, and nervous system development continue throughout childhood and adolescence and toxicity during development may lead to permanent bone, behavior, learning, and memory changes in animals and humans. Topiramate also carries a warning for acute myopia and secondary angle closure glaucoma and retinal degeneration/atrophy was increased in rats treated with phentermine and topiramate. Because both drugs act on nervous and bone systems, there are concerns that phentermine alone may cause irreversible toxicity or possibly potentiate topiramate-induced toxicity. Behavior, learning and memory, nervous system, and bone/teeth development should be assessed in juvenile animals prior to subjecting children to an unknown risk for permanent developmental toxicity. Specific endpoints that can be addressed include behavior, learning and memory, extensive histopathology of brain and spinal cord including myelination, bone growth and thickness, ophthalmoscopy and extensive ocular histopathology, standard clinical pathology and toxicity endpoints, sexual maturation, reversibility of toxicity after a drug-free period, and toxicokinetic exposure assessment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A juvenile animal study with phentermine and topiramate coadministration to assess behavior, learning and memory, (b) (4) and ocular toxicity, and general nervous system and bone/teeth development, including assessments of drug exposure and reversibility of any observed toxicity.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?

- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name:	22580 Qsymia (phentermine and topiramate extended release) capsules
PMR/PMC Description:	An <i>in vitro</i> study to determine the inhibition potential of both phentermine and topiramate individually and in combination on the following human transporters: <ul style="list-style-type: none">• organic cation transporter 2 (OCT2) and organic cation transporter 3 (OCT3)• organic anion transporter 3 (OAT3) and organic anion transporter 4 (OAT4)• multidrug and toxin extrusion protein 1 (MATE1) and multidrug and toxin extrusion protein 2-K (MATE2-K)
PMR/PMC Schedule Milestones:	Final Protocol Submission: 09/30/2012 Study/Trial Completion: 03/31/2013 Final Report Submission: 09/30/2013 Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

Qsymia is indicated for the treatment of obesity and overweight with co-morbidities and will be prescribed for, and used by, millions of patients. Dose-related increases in serum creatinine were identified in the clinical development program. This increase in creatinine may be because phentermine and topiramate decrease renal function such as glomerular filtration, or because they inhibit renal transporters. We do not know the long-term clinical consequence of the observed rise in serum creatinine. The recommended *in vitro* study will help understand the mechanism of the observed serum creatinine increase with the use of Qsymia.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The issue is the dose-related increase in serum creatinine observed with Qsymia in the clinical development program. *In vitro* data indicate that the following renal transporters transport creatinine in humans: OCT2, OCT3, OAT3, OAT4, MATE1 and MATE2-K. The goal of the proposed study is to learn whether phentermine and/or topiramate are inhibitors of human renal transporters, which help to provide a mechanism for the observed increase in serum creatinine with the use of this product.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/in vitro studies

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An *in vitro* study to determine the inhibition potential of both phentermine and topiramate individually and in combination on the following human transporters:

- organic cation transporter 2 (OCT2) and organic cation transporter 3 (OCT3)
- organic anion transporter 3 (OAT3) and organic anion transporter 4 (OAT4)
- multidrug and toxin extrusion protein 1 (MATE1) and multidrug and toxin extrusion protein 2-K (MATE2-K)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials

☐ Immunogenicity as a marker of safety

☒ Other (provide explanation)

In vitro study to assess the inhibition potential of human renal transporters by phentermine and/or topiramate

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	NDA 22580	
Product Name:	Qsymia (phentermine and topiramate extended-release) capsules	
PMR/PMC Description:	A prospective cohort study to: 1) determine the frequency of pregnancy in women of child bearing age prescribed Qsymia and 2) 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. (b) (4)	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	10/31/2012
	Interim Report Submissions:	07/31/2014
		07/31/2015
		07/31/2016
		07/31/2017
		07/31/2018
	Study/Trial Completion:	07/31/2019
	Final Report Submission:	10/31/2019
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Observational studies have shown an increased risk of oral clefts in infants exposed to topiramate during pregnancy. In these studies, most women who used topiramate during pregnancy had other medical conditions (epilepsy or migraine headache), not obesity for which Qsymia is indicated.

The frequency at which pregnancy will occur in women of childbearing age prescribed Qsymia is not yet known.

The risk of oral clefts, major congenital malformations, and low birth weight in offspring of women exposed to Qsymia (phentermine and topiramate extended-release) during pregnancy compared to similar women not exposed to Qsymia during pregnancy is also unknown.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Review issue and goal: To determine the frequency of pregnancy in women of child bearing age prescribed Qsymia and to determine the risk of oral clefts, major congenital malformations, and low birth weight in offspring of women exposed to Qsymia during pregnancy compared with offspring of similar women not exposed to Qsymia during pregnancy.

Risks will be determined through this prospective cohort study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective cohort study that: 1) determines the frequency of pregnancy in women of child bearing age prescribed Qsymia and 2) compares the risk of oral clefts, major congenital malformations, and low birth weight in offspring of women exposed to Qsymia during pregnancy compared with offspring of similar women not exposed to Qsymia during pregnancy. (b) (4)

Required

- ☒ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	NDA 22580	
Product Name:	Qsymia (phentermine and topiramate extended-release) capsules	
PMR/PMC Description:	A drug use study conducted annually for 7 years with nationally representative and projected data to provide the following about patients prescribed Qsymia: 1) the estimated total number of prescriptions and patients dispensed Qsymia per year; 2) distribution of patients by age, sex, and BMI; 3) distribution of prescribers by specialty; 4) average, median, and range for duration of use; 5) average and median size of prescriptions; 6) prescribed average daily dose; 7) frequencies of top 10 concomitant diagnoses (including pregnancy) by age and sex; 8) frequencies of top 10 concomitant drugs by age and sex (including contraceptive medications for females of childbearing age).	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	10/31/2012
	Interim Report Submissions:	07/31/2013
		07/31/2014
		07/31/2014
		07/31/2015
		07/31/2016
		07/31/2017
		07/31/2018
	Study/Trial Completion:	09/30/2019
	Final Report Submission:	12/31/2019
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Observational studies have shown an increased risk of oral clefts in infants exposed to topiramate during pregnancy. Qsymia, which contains topiramate extended-release and phentermine, is Pregnancy Category X and is contraindicated in pregnancy. Women of childbearing potential are advised to use adequate contraception while using Qsymia. The drug will have a risk evaluation and mitigation strategy (REMS) and it will be dispensed through specially certified pharmacies. A drug use study will provide estimates of the total annual number of prescriptions and patients dispensed Qsymia and descriptive information to assess appropriate use.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Review issue and goal: To determine estimates of the total annual number of prescriptions and patients dispensed Qsymia and descriptive information to assess the amount and appropriateness of Qsymia use. Qsymia will be dispensed through specially certified pharmacies.

Risks will be determined through this drug use study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☒ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A drug use study conducted annually for 7 years with nationally representative and projected data to provide the following about patients prescribed Qsymia: 1) the estimated total number of prescriptions and patients dispensed Qsymia per year; 2) distribution of patients by age, sex, and BMI; 3) distribution of prescribers by specialty; 4) average, median, and range for duration of use; 5) average and median size of prescriptions; 6) prescribed average daily dose; 7) frequencies of top 10 concomitant diagnoses (including pregnancy) by age and sex; 8) frequencies of top 10 concomitant drugs by age and sex (including contraceptive medications for females of childbearing age).

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Drug utilization study
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA #	22580
Product Name:	Qsymia (phentermine/topiramate extended release) capsules
PMR/PMC Description:	A randomized, placebo- and active-controlled trial of renal function in obese adults on (b)(4) Qsymia (3 dosage strengths). The primary objective of the trial will be to assess the change in measured GFR (assessed as urinary clearance of 125I-sodium iothalamate). Depending on the results of short-term Qsymia exposure on measured GFR, longer follow-up of affected individuals may be required.
PMR/PMC Schedule Milestones:	Final Protocol Submission: 09/30/2012
	Study/Trial Completion: 06/30/2013
	Final Report Submission: 12/31/2013
	Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

In a cohort of overweight and obese adults dose- and time-related increases in serum creatinine have been observed. Theoretical reasons for elevation in creatinine include blockade of creatinine secretion through inhibition of renal tubule transporters by Qsymia, diuretic effects of Qsymia, or most concerning, a decrease in renal function as measured by GFR. Estimated GFR calculations are primarily derived from a lean population and therefore may be less accurate when applied to an obese population. There were no significant imbalances in the number of patients with acute or chronic renal failure in the Qsymia development program to insist on a pre-approval outcome trial; however, more information on directly measured outcomes of renal function are required.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The primary objective of this study will be to characterize the effect of Qsymia treatment on renal function in obese adults without chronic kidney disease over time - on and off of Qsymia.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, placebo- and active-controlled study of renal function in obese adults without chronic kidney disease on and off Qsymia (3 dosage strengths). The primary objective of the trial will be to assess the change in measured GFR (assessed as urinary clearance of 125I-sodium iothalamate). Depending on the results of short-term Qsymia exposure on measured GFR, longer follow-up of affected individuals may be required.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

Product Name: Qsymia (phentermine/topiramate extended release) capsules

PMR/PMC Description:	A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with Qsymia on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese subjects with cardiovascular disease or multiple cardiovascular risk factors. A subset of individuals should have measurements of bone health assessed by serial radiographic and laboratory measurements. Measurements of autonomic function (heart rate variability, baroreceptor sensitivity) and dynamic testing (24-hour blood pressure and heart rate monitoring) should also be assessed in a subset of individuals.
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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/31/2012</u>
	Study/Trial Completion:	<u>06/30/2017</u>
	Final Report Submission:	<u>12/31/2018</u>
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☒ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

In a cohort of overweight and obese adults with mostly low-to-moderate baseline cardiovascular risk treated with Qsymia, the observed changes in blood pressure, rate-pressure product, and post-hoc analyses of MACE events were directionally favorable and similar to placebo. Mean heart rate increased with Qsymia treatment versus placebo, and while the differences are small, they were consistent across subgroups and were observed at the end of the 2-year treatment period. It is unknown what the clinical significance of Qsymia's cardiovascular and metabolic effects will be in a subjects at high risk for cardiovascular events treated long-term with Qsymia. Ultimately, only a long-term, cardiovascular outcome trial can define the effect of Qsymia treatment on risk for major adverse cardiovascular events in an obese at-risk population.

A decrease in serum bicarbonate is a known side effect of topiramate, a component of Qsymia. Dose-related decreases in serum bicarbonate were observed within the Qsymia clinical development program. There is evidence to suggest that chronic metabolic acidosis can lead to increased bone turnover and deterioration of overall bone health. In small observational studies, topiramate use in women with epilepsy and migraines has suggested an adverse effect on bone. Qsymia will be indicated for chronic use and longer-term data is needed to assess risk of adverse effects on bone in obese adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The primary objective of a cardiovascular outcome trial is to evaluate the effect of long-term treatment with Qsymia on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese subjects with cardiovascular disease or multiple cardiovascular disease risk factors.

A subset of individuals should have measurements of bone health assessed by serial radiographic and laboratory measurements.

Measurements of autonomic function (heart rate variability, baroreceptor sensitivity) and dynamic testing (24-hour blood pressure and heart rate monitoring) should also be assessed in a subset of individuals in the trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with Qsymia on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese subjects with cardiovascular disease or multiple cardiovascular risk factors.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other _____
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

AMY G EGAN
07/13/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)
Division of Consumer Drug Promotion (DCDP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 14, 2012

To: Pooja Dharia, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel M. Skariah, Regulatory Review Officer, DPDP

CC: Kendra Y. Jones, Regulatory Review Officer, DCDP
Lisa Hubbard, Group Leader, DPDP
Shefali Doshi, Group Leader, DCDP

Subject: NDA #022580 QNEXA[®] (phentermine/topiramate)
Labeling Review

OPDP has reviewed the proposed package insert (PI) and carton/container labeling for QNEXA[®] (phentermine/topiramate) originally consulted from DMEP on November 1, 2011. OPDP has reviewed the proposed version of the PI accessed from the eRoom on June 4, 2012 as well as the carton/container labeling submitted on April 16, 2012.

Comments regarding the PI are provided in the marked versions below. OPDP has reviewed the carton/container labeling and does not have any comments at this time.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
06/14/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Consumer Drug Promotion (DCDP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 12, 2012

To: Pooja Dharia – Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones – Regulatory Review Officer, DCDP

CC: Samuel Skariah, Regulatory Review Officer, DPDP

Subject: NDA 022580
OPDP labeling comments for TRADENAME (phentermine and
topiramate extended-release) Capsules CIV

In response to DMEP's November 1, 2011, consult request, OPDP has reviewed the proposed draft Medication Guide for Tradename (phentermine and topiramate extended-release) Capsules CIV.

Comments on the proposed draft Medication Guide are based on the substantially complete version of the Medication Guide sent via email from Shawna Hutchins (DMPP) on June 1, 2012.

Comments regarding the Prescribing Information (PI) will be provided in a separate memo at a later date.

Thank you for the opportunity to comment on this label.

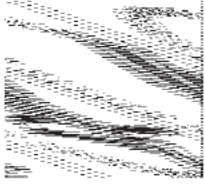
If you have any questions regarding this proposed draft Medication Guide, please contact Kendra Jones at 301-796-3917 or Kendra.Jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
06/12/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Review

Date: June 2, 2012 **Date Consulted:** November 1, 2011

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD, DABT
Acting Team Leader Pediatric and Maternal Health Staff (Maternal Health}

Hari Cheryl Sachs, MD
Medical Team Leader, Pediatric and Maternal Health Staff (Pediatrics)

Lisa Mathis, MD
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Metabolic and Endocrine Products (DMEP)
Division of Risk Management (DRISK)

Drug: Qsymia (phentermine/topiramate) Controlled Release Capsules, NDA 22-580

Sponsor: Vivus, Inc.

Subject: Review of Pregnancy, Nursing Mothers, and Pediatric Use Labeling
Review of Prescriber Counseling Tool and Patient Education Material (REMS materials related to teratogenicity)

Materials Reviewed:

- Draft revised Qsymia labeling, dated June 18, 2012
- Counseling Tool for Healthcare Providers
- Risk of Birth Defects with Qsymia (patient education material)

Consult Questions:

1. The Division of Metabolic and Endocrine Products (DMEP) requested that PMHS review and revise the pregnancy, nursing mothers, and pediatric use labeling.
2. The Division of Risk Management requested that PMHS review and revise REMS materials related to prescriber counseling and patient education.

INTRODUCTION

On October 17, 2011, Vivus, Inc. submitted a Complete Response Submission for Qsymia (phentermine/topiramate) Controlled Release Capsules, NDA 22-580, in response to the October 28, 2010, Complete Response Letter issued by the Agency. Qsymia is a fixed-dose combination of immediate-release phentermine hydrochloride beads and modified-release topiramate beads studied in the once daily doses of 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg, and is proposed for the treatment of obesity, including weight loss and maintenance of weight loss and should be used in conjunction with diet and exercise. Qsymia is recommended for 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 such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).¹

The Qsymia Complete Response Letter was issued for clinical concerns regarding teratogenicity with topiramate and cardiovascular safety with Qsymia. The re-submitted application was discussed at an Endocrinology and Metabolic Drugs Advisory Committee Meeting on February 22, 2012. The Advisory Committee members recommended approval of Qsymia, but that approval be contingent on the development of a risk evaluation mitigation strategy (REMS) for teratogenicity. A post-approval cardiovascular outcomes trial was also recommended.

The Division of Metabolic and Endocrine Products (DMEP) requested that PMHS review and revise the pregnancy, nursing mothers, and pediatric use labeling and The Division of Risk Management (DRISK) requested that PMHS review and revise REMS materials related to prescriber counseling and patient education regarding teratogenicity. PMHS completed the first part of this consult on December 20, 2011, addressing the risks associated with maternal weight and pregnancy and providing input on Vivus Inc.'s position regarding obesity as a teratogen, as well as providing consequences of oral facial clefts.

BACKGROUND AND DISCUSSION**Qsymia**

The components of Qsymia, topiramate and phentermine are both FDA-approved drug products. Topiramate, an anti-epileptic drug (AED) is approved for epilepsy and migraine prophylaxis and is classified as a pregnancy category D drug for use in pregnancy². Human pregnancy data with topiramate from several epidemiologic studies have demonstrated an increase in the risk of oral clefts with first trimester pregnancy exposure. No increased risk for overall congenital malformations was observed in these studies.

¹ See draft Qsymia labeling, submitted October 17, 2011

² See Appendix A for a summary of pregnancy category classifications

Phentermine, a sympathomimetic amine anorectic is the most commonly prescribed medication for short term use for the treatment of obesity in the U.S.³ All phentermine products labeling are currently being re-classified from a pregnancy category (b) (4) to a pregnancy category X (no benefit for use in pregnancy and potential risks) because of the current clinical guidelines⁴ for weight gain during pregnancy, and recommendation against weight loss, even in obese women.

No teratogenicity was observed in a small series of human pregnancies exposed to phentermine.⁵ Phentermine has pharmacologic activity similar to amphetamines so it is important to consider potential amphetamine vascular side effects, including vasoconstriction and a rise in blood pressure, on a pregnancy. There have been no animal or human studies conducted with phentermine to assess these effects but the effect of methamphetamine was studied in pregnant sheep.^{6,7} These studies demonstrated that methamphetamine readily crossed the placenta caused an elevation in maternal and fetal blood pressure, a decrease in fetal oxyhemoglobin saturation and pH, as well as a transient increase in umbilical vascular resistance, and a decrease in uterine blood flow accompanying these changes.

Pregnancy and Weight Gain Guidelines

Weight gain guidelines exist for pregnancy because both excessive weight gain and weight loss or poor weight gain during pregnancy have been associated with adverse maternal and fetal outcomes. The Institute of Medicine (IOM) published the following new pregnancy weight gain guidelines in May 2009, to address current research that had been conducted on the effects of weight gain in pregnancy on the health of both mother and baby:⁸

TABLE S-1 New Recommendations for Total and Rate of Weight Gain During Pregnancy, by Prepregnancy BMI

Pregpregnancy BMI	Total Weight Gain		Rates of Weight Gain* 2nd and 3rd Trimester	
	Range in kg	Range in lbs	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (< 18.5 kg/m ²)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5-24.9 kg/m ²)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0-29.9 kg/m ²)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥ 30.0 kg/m ²)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

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³ Hendricks EJ, Rothman RB, Greenaw FL. How physician obesity specialists use drugs to treat obesity. Obesity 2009 Sep;17(9):1730-5

⁴ See Appendix B for the current Institute of Medicine Pregnancy Weight Gain Guidelines

⁵ See REPROTOX® REPROTOX® is a subscription information system on environmental hazards to human pregnancy, reproduction and development developed by the Reproductive Toxicology Center for its members. REPROTOX contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development. Available through MicroMedex.

⁶ Stek A, Baker R, et al. Fetal responses to maternal and fetal methamphetamine in sheep. Amer J Obstet and Gyn 1995; Nov;173(5):1592-1598.

⁷ Stek A, Fisher B, et al. Fetal responses to maternal and fetal methamphetamine in the pregnant sheep. Amer J Obesity and Gyn 1993; Oct;169(4):888-897

⁸ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

An obligatory weight gain occurs in maternal tissues (the uterus, breasts, blood volume, and in the fetal-placental unit) during pregnancy. Weight gain in pregnancy is partly a gain in adipose tissue, accompanied by some degree of insulin resistance and other metabolic alterations that serve as an adaptive response to allow a more efficient transfer of fuels across the placenta to the fetus.

Excessive weight gain during pregnancy can lead to an increased risk of maternal insulin resistance and gestational diabetes mellitus, which can lead to fetal hyperglycemia and increased adiposity. In addition, these babies have a higher risk for childhood obesity and accompanying metabolic sequelae.⁹ Pre-pregnancy obesity is associated with an increased risk of major malformations, including neural tube defects, omphalocele, heart defects, orofacial clefts, and others. The mechanism for these observed malformations and obesity is not known but may be due to severe metabolic and hormonal alterations including hyperglycemia, elevated insulin, and elevated estrogen levels; nutritional deficits from dieting or poor quality diets; and/or diabetes.¹⁰

Despite the association between obesity and major fetal malformations, a minimum weight gain (and no weight loss) is recommended during pregnancy for all women, including those who are already overweight or obese because of the obligatory weight gain that occurs in maternal tissues during pregnancy. The metabolic consequences of weight loss in pregnancy may be associated with adverse neurodevelopmental outcomes in childhood.¹¹

PREA

Pediatric studies required under the Pediatric Research Equity Act (PREA) were discussed at a March 7, 2012 Pediatric Review Committee (PeRC) meeting. Required studies were deferred in patients ages 7 to ^(b)₍₄₎ years and waived in patients 0 to 6 years of age current clinical practice guidelines recommend against pharmacologic treatment for treatment of pediatric obesity in children < 7 years of age. Additional nonclinical studies will be required before studies can begin in the pediatric population. The PeRC recommended including known topiramate safety data in the pediatric use subsection of Qsymia labeling.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. Pregnancy registry or pregnancy surveillance information will be placed in the pregnancy subsection as well. For nursing mothers, when animal data are available, only the

⁹ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

¹⁰ Watkins M, Rasmussen S, et al. Maternal obesity and the risk for birth defects. *Pediatrics* 2003; 111:1152-58

¹¹ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

A new subsection, “Females and Males of Reproductive Potential” will be added to labeling when the PLLR publishes to provide information for these populations when there are human or animal data suggesting drug-associated adverse effects on fertility or when there are recommendations and/or requirements for pregnancy testing and/or contraception based on concerns for potential or demonstrated adverse developmental outcomes associated with drug exposure during pregnancy. When appropriate and applicable, this subsection must contain information under the subheadings Pregnancy testing, Contraception, and Infertility. This subsection will be omitted if not applicable.

Pediatric Use Labeling

The Pediatric Use subsection of labeling should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted. 21 CFR 201.57(c)(9)(iv) describes the appropriate pediatric use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

CONCLUSIONS

Labeling should adequately describe the contraindication for use of Qsymia in pregnancy and the risks and benefits of Qsymia for females of reproductive potential, as well as conveying the importance of regular pregnancy testing and the consistent use of effective contraception when sexually active with a male partner. Qsymia labeling should adequately describe that safety and effectiveness have not been established in the pediatric population and that use is not recommended because of the unknown benefit/risk profile. The known topiramate safety data should be described in the pediatric use subsection as well.

The REMS prescriber counseling tool and the patient education materials should have messages consistent with labeling, with further details provided than are presented in labeling, including a list of contraception choices.

RECOMMENDATIONS

PMHS has the following recommendations for Qsymia pregnancy, nursing mothers, pediatric use, and females of reproductive potential subsections of labeling. This labeling reflects our revisions to the Qsymia labeling in the DMEP e room as of June 22, 2012. PMHS’s revisions and recommendations for the REMS documents, Counseling Tool for Healthcare Providers and Risk of Birth Defects with Qsymia (patient education material) were reflected in the documents sent to the Sponsor on May 16, 2012, and in the DRISK interim REMS review dated May 16, 2012.

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/s/

JEANINE A BEST
07/02/2012

MELISSA S TASSINARI
07/02/2012

LISA L MATHIS
07/02/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **June 01, 2012**

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): TRADENAME (phentermine and topiramate extended-release)

Dosage Form and Route: Capsules for Oral Use

Application Type/Number: NDA 22-580

Applicant: **Vivus Inc.**

1 INTRODUCTION

On October 14, 2011, Vivus Inc., re-submitted for the Agency's review, a New Drug Application (NDA 22-580) for TRADENAME (phentermine and topiramate extended-release) Capsules, indicated as an adjunct to a reduced-calorie diet and increased physical activity for the treatment of obesity, including weight loss and maintenance of weight loss in adults with an initial body mass index (BMI) of 30 kg/m² or greater or 27 kg/m² when accompanied by weight related co-morbidities such as hypertension, type 2 diabetes mellitus, or dyslipidemia. Vivus Inc., originally submitted this NDA on December 28, 2009, but received a Complete Response (CR) letter dated October 28, 2010.

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for TRADENAME (phentermine and topiramate extended-release) Capsules.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DMEP under separate cover.

2 MATERIAL REVIEWED

- Draft TRADENAME (phentermine and topiramate extended-release) Capsules Medication Guide (MG) received on October 17, 2011, revised by the reviewing Division throughout the current review cycle, and received by DMPP on May 31, 2012.
- Draft TRADENAME (phentermine and topiramate extended-release) Capsules Prescribing Information (PI) received on October 17, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on May 31, 2012.
- Approved TOPAMAX (topiramate) comparator labeling dated July 15, 2011.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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SHAWNA L HUTCHINS
06/01/2012

MELISSA I HULETT
06/01/2012



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

Date: May 29, 2012

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of New Drugs (OND)

Through: Tarek Hammad, M.D., Ph.D., MSc, MS
Deputy Director, Division of Epidemiology 1 (DEPI1)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)

From: Diane K. Wysowski, M.P.H., Ph.D.
Epidemiology Team Leader, DEPI 1, OPE, OSE
Patricia L. Bright, M.S.P.H., Ph.D., Epidemiologist
Division of Epidemiology I, DEPI 1, OPE, OSE

Subject: Review of Sponsor's April 19, 2012, response to FDA
comments based on the interim report from the "Fetal outcomes
retrospective topiramate exposure study (FORTRESS)."

Drug Name(s): Qnexa (phentermine & topiramate)

Submission Number:

Application Type/Number: NDA 22580

Applicant/sponsor: Vivus

OSE RCM #: 2011-3522

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EXECUTIVE SUMMARY

Prior reports suggest that infants exposed to topiramate (TPM) in utero have an increased risk of oral clefts (OCs), but no statistically significant increased risk of other major congenital malformations (MCMs). TPM and phentermine are components of Qnexa – a product under consideration for FDA approval for the treatment of obesity. Given a potential risk to the fetus from TPM, the FDA requested VIVUS (the sponsor) to conduct an observational study of outcomes in offspring exposed to topiramate in the first trimester of pregnancy. The interim report based on this study “Fetal outcomes retrospective topiramate exposure study (FORTRESS),” was submitted to the FDA on December 13, 2011.

The objective of this review is to respond to the sponsor’s April 19, 2012, comments. These were generated following an FDA correspondence from February 15, 2012 based on the interim FORTRESS study report as well as based on correspondence from the sponsor dated January 11, 2012.

Recommendations to the sponsor are included in Section 3 of this review.

1 BACKGROUND

The sponsor is seeking approval for Qnexa, a combination of phentermine and TPM (two marketed products), for the treatment of obesity. If approved, Qnexa will be available in three fixed-dose combinations of phentermine/topiramate: 3.75mg/23mg, 7.5mg/46mg, and 15mg/92mg. Since prior reports suggest that infants exposed to TPM in utero have an increased risk of OCs, the Division of Metabolism and Endocrinology Products (DMEP) requested the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology I (OSE/OPE/DEPI I) to review the FORTRESS study. This protocol, dated September 6, 2011, was designed to estimate the prevalence ratio of OCs and MCMs in newborns of women exposed to topiramate during the first trimester of pregnancy. (For further study information, see the January 20, 2012, review by Julia Ju Pharm. D., Ph.D., Division of Epidemiology I [DEPI I] assessing the FORTRESS study interim report.)

Prior correspondence between the FDA and the sponsor following protocol implementation includes the following:

- The sponsor submitted an interim report dated December 13, 2011, based on the observational study “Fetal outcomes retrospective topiramate exposure study (FORTRESS).”
- On December 19, 2011, the FDA requested more study results.
- The sponsor responded on January 11, 2012.
- FDA’s comments were sent to the sponsor on February 15, 2012, concerning mother-baby dyads, prevalence ratios of OCs, distributions of study covariates within each stratum and FDA recommendations.
- The sponsor provided a response to these on April 19, 2012.

The FDA Feb 15th, 2012, comments and the April 19th, 2012, sponsor responses are listed below along with a current assessment *in italics* by DEPI1 staff.

2 COMMENTS SENT TO THE SPONSOR, RESPONSES RECEIVED, AND ASSESSMENTS

On February 15, 2012, the FDA sent comments to the sponsor based on both the interim report and subsequent correspondence from the sponsor dated January 11, 2012, related to the observational study “Fetal outcomes retrospective topiramate exposure study (FORTRESS).” These FDA comments are included below followed by the sponsor response dated April 19, 2012. Our DEPI1 assessments follow in *italics*.

2.1 FDA Feb. 15, 2012, Comment #1: Number of Mother Baby Dyads

Please obtain more mother-baby dyads for the FORTRESS study (e.g. from the Kaiser Southern California research database as proposed in the study protocol) to ensure an adequate sample size in the TPM monotherapy subcohort.

2.1.1 Sponsor Response

Although the Kaiser Southern California research database was considered initially, feasibility studies at this site showed that only approximately 50 mother-infant dyads with topiramate exposure during pregnancy could be obtained. Because there were so few dyads from this center, and because the Southern California Kaiser database operates independently from the Northern California database, it was concluded that the complexity of adding this group to the study was not justified in light of the low sample size by less than 3%, and would not meaningfully change any of the conclusions of this study.

Prior to initiation of the FORTRESS study, VIVUS has conducted a thorough feasibility study to identify potential data sources that could provide mother infant dyads for evaluation. Based on the results of this feasibility work, we included the 4 sources described in the FORTRESS protocol based on their size, their experience in conducting this type of research and their ability to work within the common protocol, and their ability to produce results under a reasonable timeline. Together, these data centers cover approximately 70 million lives. While it is always possible to find more mother-baby dyads, finding enough to significantly change the power of the FORTRESS study to demonstrate the risk of topiramate with respect to oral clefts is not feasible due to the time and resources that would be required.

2.1.2 Comments

The sponsor’s rationale is adequate -- given the small sample size of the mother-baby dyads from the Southern California Kaiser database, the addition of these dyads probably would not result in a meaningful change in any study conclusion.

2.2 FDA Feb. 15, 2012, Comment #2: Re-Assessing the Prevalence Ratios

Please re-assess the prevalence ratios of OCs and MCMs using all eligible study subjects in the SMP cohorts at all study sites and submit study results to the FDA.

2.2.1 Sponsor Response

This has been completed and was emailed to the Division on 10 February 2012.

2.2.2 Comments

This concern has been adequately addressed.

2.3 **FDA Feb. 15, 2012, Comment #3: Data on the Distributions of Study Covariates**

Please provide data on the distributions of the study covariates within each stratum with the propensity score stratification approach to the FDA to examine whether these covariates were balanced across study cohorts.

2.3.1 **Sponsor Response**

These analyses are currently ongoing and will be addressed in the final report.

2.3.2 **Comments**

We agree to the inclusion of these data as part of the final report.

2.4 **FDA Feb. 15, 2012, Comment #4: Validation of Cases**

You should validate all potential MCM cases that will be identified in the study cohorts. Alternatively, the sponsor may restrict the validation to all of the 10 most common specific MCMs. The validation should be done in the study cohorts to enhance the validity of the study results and only validated cases should be included in the final analyses. The positive predictive values (PPVs) should be estimated using both the base case definition and the secondary, more restrictive case definition. A sampling approach is not preferred because of the challenges of specifying appropriate sampling fraction and the acceptable precision margins for PPV given the heterogeneity of malformations. Additionally, low PPV values present a challenge in utilizing the validation data in estimating the risk.

2.4.1 **Sponsor Response**

It is highly unlikely that topiramate or any medication would affect the development of all types of major malformations. In consideration of this, VIVUS believes that it is not feasible, from a time and resource perspective, to validate all potential MCM cases. This is particularly true now that comparisons between the topiramate and SMP cohorts need to consider the entire SMP cohort, which contains over 250,000 dyads, and over 13,500 MCMs.

Vivus maintains that the strategy initially outlined in the FORTRESS protocol represents a reasonable and much more feasible alternative. The strategy involves developing more restrictive (and presumably, more specific) definitions for each of the individual MCMs based on clinically relevant patterns of care identified in the automated data (e.g. corrective surgery, persistence of a diagnosis after imaging, or diagnosis by a specialist). Algorithms for these definitions were developed in consultation with two academic pediatricians who routinely care for children with a spectrum of MCMs in their practice of clinical genetics. We have planned to validate a sample of approximately 300 cases with the ten most common MCMs identified using the restrictive case definition in the automated data against medical records. This approach will generate positive predictive values (PPVs) for each of these ten individual MCMs and allow us to estimate the PPV for the restrictive MCM case definition overall. We would like to clarify that the MCMs to be validated will not necessarily come from the study cohorts but rather they will come from a sample of the source data. This point has been a source of confusion throughout the history of the project.

Planned sensitivity analyses will consider the impact of PPVs generated as part of this validation on the TPM MCM association.

2.4.2 **Comments**

Although we agree that it is highly unlikely that topiramate would affect the development of all major malformations, we need to proceed with caution because we do not know which (if any)

malformations may be affected. We recognize, however, that validating all MCM cases would require significant resources since there were 11,277 total crude events as listed in Table 1 from the full SMP population.¹ Therefore, we suggest a two-step approach that would utilize the efficiencies of high PPV scores, yet maintain the rigor in case identification that validation provides for those malformations with poor PPV scores that appear to be related to Qnexa. As a first step, we agree with the sponsor's plan to validate against medical records a sample of approximately 300 cases with the ten most common MCMs (identified using the restrictive case definition in the automated data) so as to generate positive predictive values (PPVs) for each of these ten individual MCMs. As a second step, we request that the ten most common MCMs identified using the above method that are found to have a PPV of less than 70%² that appear to be related to Qnexa undergo further outcome validation. Such validation should be done in the study cohort.

Congenital malformations were identified using inpatient claims or birth certificates for three studies of congenital malformations in the Tennessee Medicaid (TennCare) population. The positive predictive values were calculated following confirmation through medical record review.³ These top 18 malformations and associated PPVs were as follows:

Order of frequency	Defect	Positive predictive value (%)
1	Abdominal wall defects	80.8
2	Patent ductus arteriosus	64.3
3	Polydactyly	91.8
4	Atrial septal defect	82.1
5	Ventricular septal defect	71.5
6	Pyloric stenosis	86.4
7	Obstructive genitourinary defect	68.9
8	Hypospadias	91.4
9	Hydrocephaly	34.3
10	Cleft lip or cleft palate	93.1
11	Congenital hip dysplasia	34.7
12	Pulmonary valve stenosis	43.2
13	Renal dysgenesis	67.6
14	Microcephaly	71.0
15	Transposition of the great vessels	74.1
16	Stenosis/atresia of the large intestine	72.0
17	Coarctation of the aorta	70.8
18	Reduction defects upper limbs	52.9

In the above sample, we would ask that those in the top ten with case definitions PPVs of less than 70% (e.g. patent ductus arteriosus, obstructive genitourinary defect, and hydrocephaly) and that appear related to Qnexa undergo a confirmatory chart review. The above database had a total of 1,430 potential congenital malformations of which 1,316 were identified from inpatient claims. Of the 1,430, the number of those in the top ten and with PPVs of less than 70% was 367. Although the list of top ten malformations and PPV scores generated from the sponsor would be different from that above due to a different patient population, different database, and different case definitions, such an approach would provide additional validation rigor for the more common malformations that appear related to Qnexa in the absence of high PPV scores.

2.5 FDA Feb. 15, 2012, Comment #5: Propensity Score Stratification

The propensity score stratification analysis is preferred over the stratified analysis by individual covariate and the strata should be classified by quartiles instead of deciles of propensity score distribution. A sensitivity analysis using propensity score matching should be performed.

2.5.1 Sponsor Response

Propensity score matching should give the same result as stratifying by decile of propensity score, given the trimming that has been done to the distributions before stratification. Therefore the analysis using propensity score matching is not needed. A reanalysis that stratifies by quartiles of propensity score rather than deciles is more likely to lead to residual confounding, although it in principle could result in narrower confidence intervals. On balance we believe that we have sufficient data to support the decile stratification and the quartile stratification would be inadvisable, although the results would likely be close to what is now reported for the decile stratification.

2.5.2 Comments

Although stratifying by deciles poses a concern due to low counts, we will not require a re-analysis by quartiles.

2.6 FDA Feb. 15, 2012, Comment #6: Inclusion of Infant Sex in the Regression Model

Infant sex should not be included in the logistic regression model to generate propensity scores as this is not a factor affecting the probability of a mother using TPM during early pregnancy.

2.6.1 Sponsor Response

We agree that it is unlikely (though not impossible) that infant sex is associated with use of TPM during early pregnancy. Nevertheless, variables unassociated with exposure but associated with outcome have been shown to improve the control of confounding in propensity score models (ref: Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T: Variable selection for propensity score models. Am J Epidemiol. 2006; 163:1149-1156), and thus we do not believe that re-analyzing the data for this reason would be indicated.

2.6.2 Comments

We agree to the approach outlined by the sponsor.

3 RECOMMENDATIONS TO THE SPONSOR

Recommendation #1: Number of Mother-Baby Dyads

- We believe that you have provided sufficient justification to leave out the mother-baby dyads from the Southern California Kaiser database.

Recommendation #2: Re-Assessing the Prevalence Ratios

- We concur with your assessment of prevalence ratios.

Recommendation #3: Data on the Distribution of Study Covariates

- We agree that these data should be included as part of the final report.

Recommendation #4: Validation of Cases

- We recommend that you incorporate a subsequent step following validation of a sample of cases and generation of PPV scores. Recognizing that validating all MCM cases would require significant resources -- 11,277 total crude events as listed in Table 1 analysis from the full SMP population, you could implement your proposal to validate a sample of approximately 300 cases with the ten most common MCMs identified using the restrictive case definition in the automated data. This validation can then be used to generate positive predictive values (PPVs) for each of the ten individual MCMs as planned. As a second step, we request that the ten most common MCMs identified using the above method that are found to have a PPV of less than 70% and that appear related to Qnexa undergo validation in the study cohort using medical records. (The following reference may be helpful: Cooper WO, Hernandez-Diaz S, Gideon P, et al. Positive predictive value of computerized records for major congenital malformations. *Pharmacoepidemiology and Drug Safety* 2008; 17:455-460.)

Recommendation #5: Propensity Score Stratification

- We agree that it is not necessary to conduct a re-analysis by quartiles although stratifying by deciles poses a concern due to low counts.

Recommendation #6: Inclusion of Infant Sex in the Regression Model

- We agree that you have provided sufficient justification to leave infant sex in the model.

CC: Bright P/Calloway P/Zerislassie E/Wysowski D/Hammad T/Iyasu S/DEPI1/OSE
Egan A/ Hai M/ Roberts M/ Pooja D/ Craig E/ Colman E/Parks M/DMEP/OND

4 REFERENCES

¹ From sponsor's submission of updated counts among the universe of women who met the criteria for the FORTRESS Similar Medical Profile (SMP) cohort from 3 centers.

² Carnahan, RM. Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative data: summary of findings and suggestions for future research. *Pharmacoepidemiology and Drug Safety* 2012; 21(S1):90-99.

³ Cooper WO, Hernandez-Diaz S, Gideon P, et al. Positive predictive value of computerized records for major congenital malformations. *Pharmacoepidemiology and Drug Safety* 2008; 17:455-460.

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/s/

PATRICIA L BRIGHT
05/29/2012

DIANE K WYSOWSKI
05/29/2012

TAREK A HAMMAD
05/29/2012

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

Pharmacovigilance Review

Date: March 8, 2012

Reviewer(s): Selena Ready, Pharm.D., Safety Evaluator
Sarita Boyd, Pharm.D., Safety Evaluator
Carolyn J. Tabak, M.D., M.P.H., Medical Officer
Division of Pharmacovigilance I
Office of Surveillance and Epidemiology

Team Leader(s): Lanh Green, Pharm.D, M.P.H.
Allen Brinker, M.D., M.S.
Division of Pharmacovigilance I
Office of Surveillance and Epidemiology

Division Director: Linda Scarazzini, M.D., RPh
Division of Pharmacovigilance I

Product Name(s): Phentermine/Topiramate (QNEXA)

Subject: Abuse, Misuse, or Dependence

Application Type/Number: NDA 22-580

Applicant/Sponsor: Vivus, Inc

OSE RCM #: 2012-230

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EXECUTIVE SUMMARY

Vivus is seeking approval of NDA 22-580, QNEXA, which is a combination of two FDA-approved products, phentermine (PHEN) and topiramate (TPM), to be used in the management of weight loss. The Controlled Substance Staff (CSS) requested this review to assist in their evaluation of Section 9 (Drug Abuse and Dependence) of the proposed label of QNEXA. Under the Controlled Substances Act (CSA), phentermine is classified as a Schedule IV stimulant. Topiramate is not currently scheduled under the CSA.

We evaluated adverse event reports from the Adverse Event Reporting System (AERS) database and literature for the time frames specified for reports of possible abuse, misuse, or dependence associated with the use of phentermine and topiramate, alone or in combination use.

Both the AERS database and medical literature contained cases of topiramate associated misuse and abuse. In the AERS case series of topiramate use without phentermine, all 22 cases were from the US and the majority of the users were relatively young and reported use for unapproved indications. Among these 22 cases, a 54-year-old man was involuntarily hospitalized to the psychiatric unit for abuse evaluation, and he refused to discontinue topiramate use after discharge. There were 7 cases of misuse for various reasons that are related to possible pharmaceutical thrill-seeking and experimentation. Diversion did occur in 6 cases in patients aged 12 to 28, a patient population which is consistent with current literature regarding diversion and misuse of pharmaceuticals.⁷ The remaining 14 cases experienced withdrawal symptoms in which patients abruptly discontinued topiramate (n=9) or were tapering the dose of topiramate (n=5). The potential for withdrawal seizures in patient's using antiepileptic drugs is well documented in the Topamax labeling and can occur in patients with or without previous history of seizure disorder.

Phentermine is a stimulant approved for the short-term treatment of obesity in 1959. It is currently scheduled IV under the CSA. A broad AERS and literature search for any adverse event with phentermine use alone yielded no new safety signals associated with abuse, misuse, or dependence.

For the combination use of phentermine and topiramate, we did not identify additional cases of concern since the May 2011 review, which did not identify any case reports of drug abuse or dependence with combination therapy.

Overall, we found no cases of new concern related to abuse, misuse, or dependence with either product, either alone or in combination based on a review of spontaneous cases and a review of the published medical literature.

1 INTRODUCTION

The Controlled Substance Staff (CSS) requested this review to assist in their evaluation of Section 9 (Drug Abuse and Dependence) of the proposed label for NDA 22-580 (QNEXA), a combination product of phentermine and topiramate (PHEN/TPM) to be used in the management of weight loss. Thus, this review evaluates reports from the Adverse Event Reporting System (AERS) database for possible abuse, misuse, or dependence associated with the use of phentermine and topiramate, alone or in combination use.

In our efforts to support CSS in the short time frame of the consult, CSS and DPV1 agreed to combine three AERS data evaluations. This review will include: A) a review of individual AERS reports on topiramate use alone, B) an update to a recent review of AERS for phentermine use alone from the data lock point in RCM# 2011-1851, in addition to reviewing of 63 reports with MedDRA Preferred Terms of overdose (accidental and intentional), suicide, and abuse captured in RCM# 2011-1851 (Appendix D), and C) an update to the review of AERS data for concomitant use of topiramate and phentermine from the data lock point in RCM# 2010-500 (Appendix E).

1.1 BACKGROUND

Vivus is seeking approval of NDA 22-580, QNEXA, which is a combination of two products, phentermine (PHEN) and topiramate (TPM). If QNEXA is approved, it will be available in full dose (15mg PHEN/92mg TPM), mid-dose (11.5mg PHEN/60mg TPM), mid-dose (7.5mg PHEN/46mg TPM) and low-dose (3.75mg PHEN/23mg TPM) for the following:

Treatment of obesity, including weight loss and maintenance of weight loss and should be used in conjunction with diet and exercise. PHEN/TPM 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)

Topiramate (Topamax) is an anti-convulsant approved for the management of epilepsy in 1996 and migraine prevention in 2004. However, TPM is also used off-label for treatment of mood disorders and neuropathic pain¹ and weight loss in combination with phentermine². Phentermine is a sympathomimetic approved for the management of weight loss in 1959. Under the Controlled Substances Act (CSA)³, phentermine is classified as a Schedule IV stimulant and contains language in the label concerning possible abuse and dependence potential.³ Topiramate is not currently scheduled under the CSA.

¹ Finocchi C, Villani V, Casucci G. Therapeutic strategies in migraine patients with mood and anxiety disorders: clinical evidence. *Neurol Sci.* 2010 Jun;31 Suppl 1:S95-8.

² Cohen PA. Phentermine plus topiramate in the treatment of obesity. *Lancet.* 2011 Jul 9;378(9786):126; author reply 126-7.

³ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=1308&showFR=1>

1.2 PRODUCT LABELING

Table 1 provides an overview of the relevant labeling sections for phentermine and topiramate.

Table 1. Approval Dates and Comparison of Relevant Labeling Sections for Phentermine and Topiramate				
Generic Name (Brand)	Phentermine Resin (Ionamin)	Phentermine HCl (Fastin)	Phentermine ODT (Suprenza)	Topiramate (Topamax)
NDA	11-613	17-352	202088	20-404, 20-844
Initial Approval Date	1959	1973	2011	1996
Indication				
Epilepsy		---		Yes
Migraine		---		Yes (prophylaxis)
Weight Loss		Yes (short term use)		No
Warnings and Precautions (related to abuse, misuse, dependence)	-Only short term monotherapy -If tolerance develops, stop drug. Do not exceed recommended dose. -Caution with driving or operating machinery -Possibility of adverse interaction with alcohol -Drug dependence (phentermine related to amphetamines and other drugs of abuse) -Not recommended for patients under 16 years of age			-Increased risk of suicidal behavior and ideation -Cognitive dysfunction, behavioral disturbances, somnolence or fatigue may occur -Gradually withdraw topiramate to minimize potential for seizures -In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including TOPAMAX®, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency
9 DRUG ABUSE AND DEPENDENCE	9.2 Abuse - Phentermine is related chemically and pharmacologically to the amphetamines. Amphetamines and other stimulant drugs have been extensively abused and the possibility of abuse of phentermine should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. 9.3 Dependence - Abuse of amphetamines and related drugs may be associated with intense psychological dependence and severe social dysfunction. There are reports of patients who have increased the dosage of these drugs to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic			- The abuse and dependence potential has not been evaluated in human studies

Table 1. Approval Dates and Comparison of Relevant Labeling Sections for Phentermine and Topiramate

Generic Name (Brand)	Phentermine Resin (Ionamin)	Phentermine HCl (Fastin)	Phentermine ODT (Suprenza)	Topiramate (Topamax)
	intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes. A severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.			
10 OVERDOSAGE	- The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose. 10.1 Acute Overdosage -Manifestations of acute overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, and panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmia, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Overdosage of pharmacologically similar compounds has resulted in fatal poisoning usually terminates in convulsions and coma.			-Overdoses of TOPAMAX® have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving TOPAMAX®.
14 CLINICAL STUDIES				14.3 Migraine Prophylaxis For patients withdrawing from Topamax, daily dosages were decreased in weekly intervals by 25 to 50 mg/day
CSA Schedule	IV			None

2 METHODS AND MATERIALS

2.1 CASE SELECTION

A. Topiramate without phentermine. For the purposes of this review, the term “abuse” refers to a pattern of misuse or overuse of a drug without regard to health concerns. “Misuse” refers to the use of a drug for an unintended purpose or intended purposes but in unapproved doses. Dependence was evaluated based upon emotional and physical withdrawal symptoms reported.

B. Phentermine without topiramate. All spontaneous reports of patients taking phentermine alone and not in combination use with fenfluramine or dexfenfluramine at the time of event were included.

C. Topiramate and phentermine concomitantly. We included spontaneous reports of patients taking both topiramate and phentermine but not fenfluramine or dexfenfluramine at the time of event. We excluded reports that were included in the previous review (RCM 2010-500).

2.2 AERS SEARCH STRATEGIES

A. Topiramate without phentermine. The Adverse Event Reporting System (AERS) was searched for topiramate use only with the strategy described in Table 2.

Table 2. AERS Search Strategy* - Topiramate without phentermine	
Date of search	February 7, 2012
Time period of search	December 24, 1996 [^] – January 31, 2012
Product Terms	Topamax [®] ; Topiramate; Topir%
MedDRA Search Terms	PT Terms: Dependence, Drug abuse, Drug and chemical abuse, Drug dependence, Drug dependence-antepartum, Drug dependence-postpartum, Drug tolerance, Drug tolerance increased, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal maintenance therapy, Drug withdrawal syndrome, Drug withdrawal syndrome-neonatal, Intentional drug misuse, Neonatal complications of substance abuse, Needle track marks, Overdose, Polysubstance dependence, Substance abuse, Tachyphylaxis, Withdrawal arrhythmia, Withdrawal syndrome
Countries	US Only
Outcome	Serious [§]

* See Appendix A for description of the AERS database.

[^] US Approval date

[§] Death, Hospitalized, Disability, Life-threatening, Congenital Anomaly, Other Serious

B. Phentermine without topiramate. The Adverse Event Reporting System (AERS) was searched for phentermine use only with the strategy described in Table 3.

Table 3: AERS Search Strategy* - Phentermine without topiramate	
Date	February 21, 2012
Time period	May 27, 2011 – January 31, 2012
Drug Names	Trade: Adipex-P, Ionamin, Fastin, Suprenza, Tora Active Ingredient: phentermine Verbatim Substance Name: phenter%
MedDRA Search Terms	All
Countries	US Only
Outcome	Serious [§]
Reporter Source	Health Professional; Literature

* See Appendix A for description of the AERS database.

[^] Reporter Source was restricted to match the search strategy performed in RCM #2011-1851

[§] Death, Hospitalized, Disability, Life-threatening, Congenital Anomaly, Other Serious

C. Topiramate and phentermine concomitantly. The Adverse Event Reporting System (AERS) was searched for phentermine and topiramate taken concomitantly with the strategy described in Table 4.

Table 4. AERS Search Strategy* - Phentermine and Topiramate Concomitantly	
Date of search	February 10, 2012
Time period of search	January 1, 2010 – January 31, 2012 [^]
Product Terms	Interaction Search (Concomitant Products) Product 1: Topiramate (Topamax)

	Product 2: Phentermine (Adipex-P, Ionamin, Fastin)
MedDRA Search Terms	All [†]
Countries	All (Domestic and Foreign)
Outcome	All (Serious and Non-serious)

* See Appendix A for description of the AERS database.

^ Search dates were selected to update the previous review (RCM 2010-500).

† Search terms were broad to match the previous review (RCM 2010-500) and because total number of reports with concurrent use was expected to be low.

2.3 LITERATURE SEARCH

A. Topiramate without phentermine. The medical literature was searched for topiramate use only with the strategy described in Table 5.

Table 5. Literature Search Strategy – Topiramate without phentermine	
Date of search	February 7, 2012
Database	PubMed@FDA; Google
Search Terms	Addiction or Dependence and Topiramate
Years included in search	Last 5 years
Language	English

B. Phentermine without topiramate. The medical literature was searched for phentermine use only with the strategy described in Table 6.

Table 6. Literature Search Strategy – Phentermine without topiramate	
Date of search	February 20, 2012
Database	PubMed@FDA; Google
Search Terms	Addiction or Dependence and Phentermine
Years included in search	Last 5 years
Language	English

C. Topiramate and phentermine concomitantly. The medical literature was searched for phentermine and topiramate use concomitantly with the strategy described in Table 7.

Table 7. Literature Search Strategy – Phentermine and Topiramate Concomitantly	
Date of search	February 14, 2012
Database	PubMed@FDA
Search Terms	Addiction or Dependence and Phentermine and Topiramate
Years included in search	Last 5 years
Language	English

3 RESULTS

3.1 AERS CASE SELECTION

A. Topiramate without phentermine. The AERS database search for topiramate use alone captured 304 reports. A total of 282 reports were not included in the final analysis (see Figure A). The remaining 22 cases were included in the case series of abuse, misuse, or dependence reported with topiramate use.

Figure A. AERS Case Selection – Topiramate without phentermine

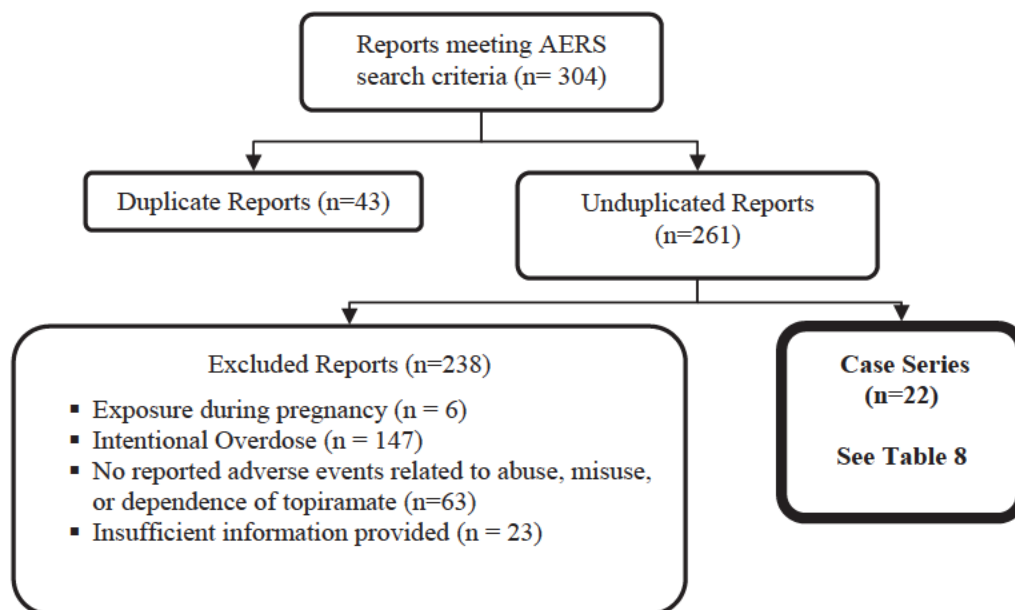


Table 8 summarizes the 22 AERS cases of drug abuse, misuse, or dependency reported with topiramate for this case series.

Table 8. Descriptive Characteristics of Domestic AERS Cases Associated With Topiramate and without phentermine received by the FDA from Product Marketing Date Through January 31, 2012 (n=22)		
Characteristic		
Age (yrs)		
Median: 38	10-19	5
Range: 12-73	20-29	3
n=20	30-39	4
	40-49	5
	50+	3
	Age not reported	2
Gender		
	Female	14
	Male	8
Reported Topiramate Indication and Dose		
	Bipolar Affective Disorder (unapproved)	2
	- Daily dose (mg): 100 (1), 300 (1)	

Table 8. Descriptive Characteristics of Domestic AERS Cases Associated With Topiramate and without phentermine received by the FDA from Product Marketing Date Through January 31, 2012 (n=22)

Characteristic	
Migraine (approved)	10
- Daily dose (mg): 25 (1), 50 (1), 100 (2), 175 (1), 200 (1), 300 (1), 800 (1), Unreported (2)	
Bipolar Affective Disorder + Migraine + Peripheral Neuropathy (unapproved)	1
- Daily dose (mg): 1600 (1)	
Seizure/Epilepsy (approved)	1
-Daily dose (mg): Unreported (1)	
Weight Loss (unapproved)	2
-Daily dose (mg): 200 (2)	
Use Without a Prescription/Street Use	6
-Daily dose (mg): 50 (1), 400 (2), 500 (1), 800 (1), Unreported (1)	
Reported Medical History	
Yes	11
No	11
Reported Concomitant Medications	
Yes	14
No	8
Treatment Withdrawal Symptoms Reported (n=14)	
Emotional	
insomnia n=2, panic attacks n=2, aggressiveness n=1, anxiety n=1	
Physical	
seizure n=8, "burning skin" n=1, vomiting n=1, delirium n=1, confusion n=1, skin crawling n=1, sweating n=1, flu-like symptoms n=1, "drug-seeking" behavior n=1, shakes n=1, tremors n=1, nightmares n=1, dizziness n=2, auditory hallucinations n=1, and delusions n=1	
Time to Event	
<24 hrs (n=2), 1 day (n=2), 3 days (n=1), 5 days (n=1), 6 days (n=1), 7 days (n=1), 23 days (n=1), Unreported (n=5)	
Reporter Source	
Consumer	10
Healthcare provider	12

Appendix B lists all the AERS case numbers, AERS ISR numbers and Manufacturer Control numbers for the 22 topiramate cases without phentermine in this case series.

Overview of Topiramate Cases (n=22)

There was one report of abuse of topiramate:

- ISR# 3853307 reported (by a psychiatrist) a 54-year-old male was prescribed topiramate 50mg/day for migraines and self increased his dose to 200mg/day to “keep the effect” because he needed less sleep, felt euphoric, “closed large business deals making large sums of money.” The patient was involuntarily hospitalized to the psychiatric unit for an evaluation. The topiramate was discontinued. After discharge, the patient was instructed by his psychiatrist to discontinue topiramate. However, the patient refused to comply and refused to see the prescribing physician for follow-up. The patient was taking methysergide (Sansert) concomitantly.

There were 7 cases reporting misuse of topiramate:

- ISR# 4357256 reported a teenager of unknown age who took 500mg of topiramate that she received from a friend. She experienced seizures, was hospitalized and later discharged. Outcome was not provided
- ISR# 4820796 reported a 13-year-old male who took topiramate 400mg “from my friend to get a buzz”
- ISR# 5568102 reported a 45-year-old male taking topiramate 25mg/day for weight-loss took 8 times the prescribed dose (200mg) for reason unknown and experienced word-finding difficulty. The patient was remorseful and continues to take topiramate 25mg/daily. The outcome was reported as still unresolved.
- ISR# 5098223 reported a 28-year-old male who took topiramate obtained “on the street” and experienced drug-induced secondary angle glaucoma, which resolved.
- ISR# 5767080 reported from a police officer regarding a 16-year-old female who took “4 or 5” topiramate obtained from another student over the weekend at a party.
- ISR# 6955688 literature case reported an adolescent female took 800mg of topiramate for the purpose of “getting high”
- ISR# 7941264 reported that a mother was giving unprescribed topiramate 50mg/day to her 12-year-old son for an unreported reason. It was unreported if the mother was prescribed topiramate or why the mother had possession of the topiramate.

Additionally, there were 14 cases (indicated for bipolar disorder n=2; migraine n=8; bipolar & migraine n=2; tonic-clonic seizures n= 1; weight-loss n=1) of withdrawal symptoms in which patients abruptly discontinued topiramate (n=9) or were tapering the dose of topiramate (n=5). One of the 14 cases was a published literature report of treatment withdrawal associated with topiramate:

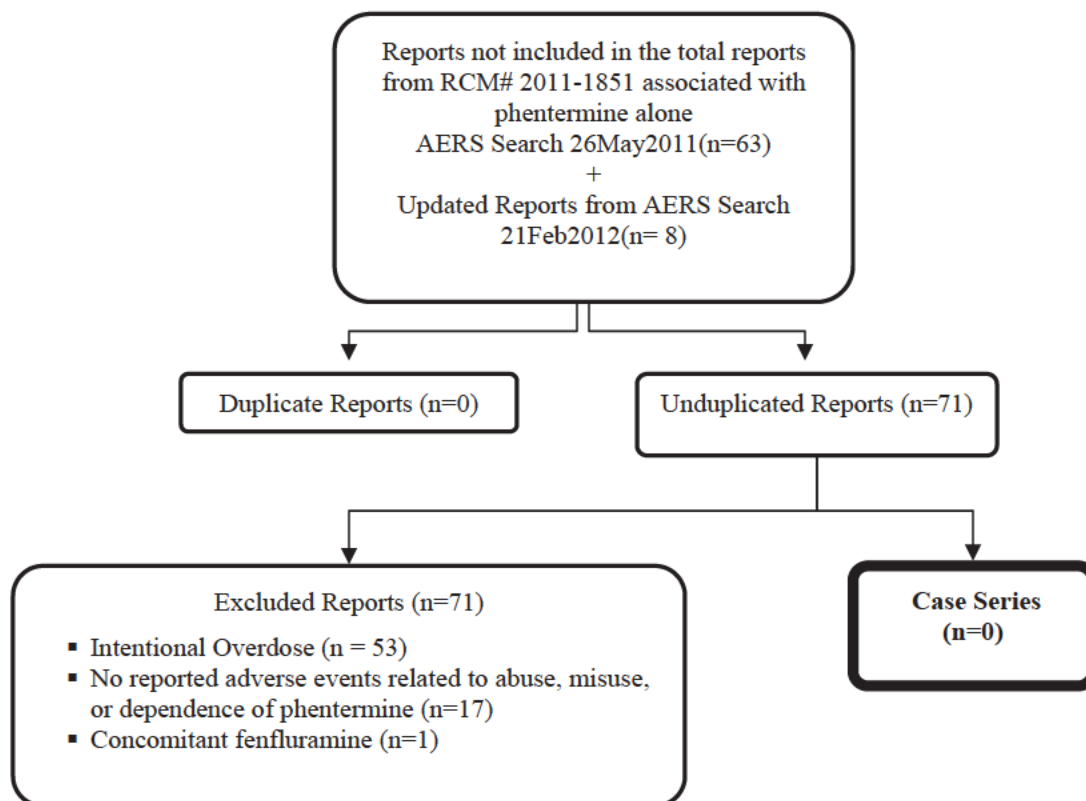
- ISR # 6327621 -Rapid onset of florid psychotic symptoms during video-EEG telemetry: undetected complex partial status? *Epilepsia*. 2009 Jan;50(1):159-60⁴.
This literature report originated from United Kingdom. A 39-year-old female experienced psychotic disorder due to a complex partial status epilepticus or a withdrawal reaction following a reduction in doses of carbamazepine and topiramate administered for tonic-clonic seizures. The author commented that “the rapid reduction of anti-epileptic drugs

⁴ Poole NA, Macdonald BK, Agrawal N. Rapid onset of florid psychotic symptoms during video-EEG telemetry: undetected complex partial status? *Epilepsia*. 2009 Jan;50(1):159-60.

in our case may have precipitated non-convulsive simple or complex partial status. The patient's history and presentation point most convincingly to this being a case of complex partial status not identified by scalp EEG, or a withdrawal syndrome."

B. Phentermine without topiramate. Using the MS Excel data from the RCM# 2011-1851 (located in Appendix E) AERS search performed on May 26, 2011, 63 reports with PT terms of overdose (accidental and intentional), suicide, and abuse were captured. After applying the case definition in Section 2 and accounting for duplicate reports, no reports were included in the review of adverse events reported with the use of phentermine. An update of AERS search, performed on February 21, 2012, for phentermine use alone retrieved 8 reports. After applying the case definition in Section 2 and accounting for duplicate reports, no reports were included in the review of adverse events reported with the use of phentermine (See Figure B).

Figure B. AERS Case Selection – Phentermine without topiramate



There were no reported cases of adverse events related to abuse, misuse, or dependence associated with phentermine use without topiramate in this review.

C. Topiramate and phentermine concomitantly. The AERS search update for phentermine and topiramate use concomitantly retrieved 27 reports. After applying the case definition in Section 2 and accounting for duplicate reports, 8 cases were included in the case series of adverse events reported with concurrent use of phentermine and topiramate (see Figure C).

Figure C. AERS Case Selection - Phentermine and Topiramate Concomitantly

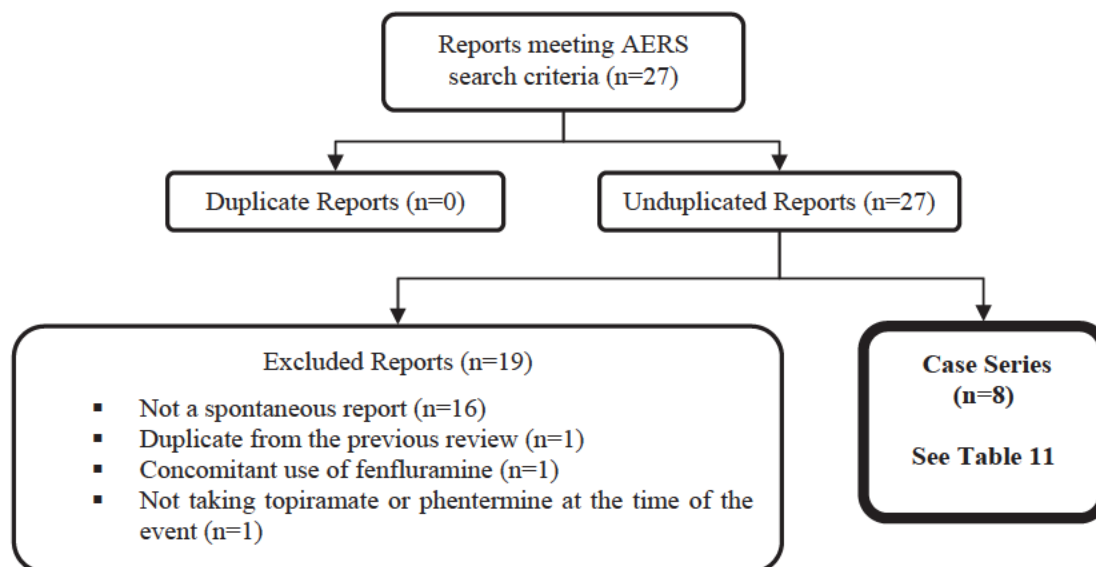


Table 11 summarizes the eight AERS cases with concurrent use of phentermine and topiramate for this case series.

Table 11. Descriptive Characteristics of Domestic AERS Cases Associated with Concurrent Use of Phentermine and Topiramate Received by FDA from January 1, 2010 – January 31, 2012 (n=8)		
Age (years) (n=8)	Mean: 43 Median: 43 Range: 20 – 57	
Gender	Female	8
Weight (kg) (n=5)	Mean: 81 Median: 82 Range: 64 – 100	
Phentermine Dose (mg)	Range: 18.75 – 37.5	3
	Unknown	6
Phentermine Indication	Weight Loss	4
	Unknown	4
Topiramate Dose	Unknown	8
Topiramate Indication	Migraine	2

Table 11. Descriptive Characteristics of Domestic AERS Cases Associated with Concurrent Use of Phentermine and Topiramate Received by FDA from January 1, 2010 – January 31, 2012 (n=8)		
Adverse Event(s)	Weight loss	3
	Unknown	3
	Abnormal behavior, Abdominal discomfort, Alopecia, Condition aggravated, Crying, Hot flush, Hypoaesthesia oral, Hypomenorrhoea, Intervertebral disc protrusion, Nausea, Nerve compression, Oral discomfort, Pain, Parasthesia oral, Pelvic pain, Stomatitis, Vulvovaginal mycotic infection, Wrong technique in drug usage process	
Outcome	Non-serious	7
	Other serious	1
Concomitant Medications	No	1
	Yes	7
Reporter Source	Consumer	6
	Health Professional	2

Overview of Phentermine and Topiramate Use Concomitantly Cases (n=8)

Of the eight AERS cases associated with concurrent use of phentermine and topiramate, seven cases reported both drugs as concomitant drugs, meaning the reporter did not suspect either drug caused the event.

Phentermine was a suspect drug in one case. A consumer reported that his wife experienced abnormal behavior while taking phentermine and two other medications, one of which he “thinks” was topiramate, for weight loss. The consumer believes the medications caused his wife to change her behavior so much that it ruined their marriage of 17 years. Of note, past medical history was significant for abuse of diet pills, including ephedrine. No serious adverse events were reported.

Appendix D lists all the AERS case numbers, AERS ISR numbers, and Manufacturer Control numbers, as well as, additional information for all included and excluded cases.

3.2 LITERATURE SEARCH (INCLUDING BOTH STUDY REPORTS AND CASE REPORTS)

A. Topiramate without phentermine. The following study counts were obtained for topiramate use without phentermine:

Topiramate and abuse:	107
Topiramate and dependence:	51
Topiramate and withdrawal:	38

Approximately 15 of these abstracts were not available, so for these, only the titles were reviewed. Of the abstracts that were available, all were reviewed.

In the initial overview, the vast majority of abstracts addressed use of topiramate as a treatment for addiction or dependence for several different drugs of abuse including alcohol, cocaine, and tobacco. No abstracts mentioned dependence or addiction as a consequence of topiramate use. Because no abstracts suggested dependence or addiction as a consequence of topiramate therapy, no full studies were reviewed.

Additionally, Google was searched using a similar, though less formal, strategy. This was done to find reports of dependence or addiction as a consequence of topiramate use by the patients themselves. Again, nothing of significance was noted.

Finally, the NIH PubMed database was searched for any articles published about topiramate in the last 90 days. This revealed two articles, neither of which had to do with addiction to topiramate.

B. Phentermine use without topiramate. We did not find any published case reports of any adverse event with phentermine use with or without topiramate.

C. Topiramate and phentermine. We did not find any published case reports of any adverse event with concurrent use of phentermine and topiramate.

4 DISCUSSION

The case series described herein includes cases of abuse, misuse, or dependence associated with the use of topiramate without concurrent therapy with phentermine. All cases were from the US and the majority (17/22) of the users were relatively young, aged 12 to 49. Over half of the cases (12/22) reported topiramate usage for other than the FDA-approved indications, seizure and migraine. Many of the cases (14/22) reported multiple concomitant medication use, such as antidepressants, anticonvulsants, and other migraine prophylaxis. There was one case report from a psychiatrist describing symptoms of topiramate abuse in which the patient self-increased his dose and refused to discontinue after his psychiatrist advised, even though he was involuntarily hospitalized in the psychiatric unit for threatening violence at home. However, the patient was taking methysergide (Sansert) concomitantly for headaches, making it a challenge to attribute the causality to topiramate alone. It's plausible that topiramate in combination with methysergide had a synergistic euphoric effect which influenced the patient. Euphoria was an infrequent adverse event that occurred in the Topamax clinical trials⁵ and mild euphoria is listed as an adverse effect with methysergide.⁶

⁵ Ortho-McNeil-Janssen Pharmaceuticals, Inc. Topamax: prescribing information. 2009. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

⁶ <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=973&CFID=39941016&CFTOKEN=8596a039c3aeb875-7308FB9E-B57C-14DC-93AC7BE86DDE0B19&jsessionid=84309cd1da8989c103402e3411241a543a6c> (accessed February 28, 2012)

The AERS cases of misuse are consistent with possible pharmaceutical thrill-seeking and experimentation. Diversion did occur with topiramate in 6 cases in patients aged 12 to 28, a patient population which is consistent with current literature regarding diversion and misuse of pharmaceuticals. Adolescents, young adults, and illicit drug users are among populations where problematic use and abuse may be most likely to occur.⁷ Like other AEDs, topiramate can cause impaired cognitive and neuropsychiatric functioning, which may be attractive for individuals who seek to experiment with FDA-approved drug products.

Treatment withdrawal symptoms occurred in 14 cases who took topiramate for migraine (n= 8), seizures (n=1) and other unapproved indications (n=6). The potential for withdrawal seizures in patient's using AEDs is well-documented in the Topamax labeling and can occur in patients with or without previous medical history of seizure disorder.⁵ Eight of the topiramate cases reported withdrawal seizures in patients who had no previous medical history of seizure disorder or epilepsy. Of the eight withdrawal seizure cases, five cases reported abrupt topiramate discontinuation and three reported a taper regime, although the length of taper was not reported. The speed of taper may have played a role in the withdrawal seizures. However, due to the lack of information in the reports it is difficult to determine.

Phentermine is a stimulant that was approved for the short-term treatment of obesity in 1959. It is currently scheduled IV under the CSA and contains language in the label concerning possible abuse and dependence potential. A broad AERS and literature search for any adverse event with phentermine use alone yielded no cases of concern associated with abuse, misuse, or dependence.

Individually, both phentermine and topiramate have been approved products and marketed in the United States for many years. However, little is known about the post-market safety profile when phentermine and topiramate are used concurrently. Similar to the earlier AERS review completed in May 2011 (Appendix E), this review retrieved no case reports of drug abuse or dependence with combination therapy. No serious adverse events were reported in the three cases in which phentermine and topiramate were both used for weight loss or in the two cases in which topiramate was used for migraines; the dose for the indication of migraines (100mg) is similar to the proposed full dose for weight loss (92mg). The cause of adverse events in seven of eight cases was possibly associated with comorbidities or concomitant medications other than phentermine or topiramate. One case lacked sufficient data to determine the role of phentermine and topiramate. Overall, we found no cases of new concern related to abuse, misuse, or dependence.

5 CONCLUSION

Based on the AERS data and published medical literature reviewed above, there were no new concerns related to abuse, misuse, or dependence with either topiramate or phentermine, either alone or in combination.

⁷ Kaye S, Darke S. The diversion and misuse of pharmaceutical stimulants: what do we know and why should we care? *Addiction*. 2012 Mar;107(3):467-77.

6 RECOMMENDATIONS

DPV 1 recommends that the labeling language for Section 9 (Drug Abuse and Dependence) of the proposed label of QNEXA remain consistent with the current language for the individually FDA-approved products, topiramate and phentermine.

7 REFERENCES

1. Finocchi C, Villani V, Casucci G. Therapeutic strategies in migraine patients with mood and anxiety disorders: clinical evidence. *Neurol Sci.* 2010 Jun;31 Suppl 1:S95-8.
2. Cohen PA. Phentermine plus topiramate in the treatment of obesity. *Lancet.* 2011 Jul 9;378(9786):126; author reply 126-7.
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4. Poole NA, Macdonald BK, Agrawal N. Rapid onset of florid psychotic symptoms during video-EEG telemetry: undetected complex partial status? *Epilepsia.* 2009 Jan;50(1):159-60.
5. Ortho-McNeil-Janssen Pharmaceuticals, Inc. Topamax: prescribing information. 2009. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>
6. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=973&CFID=39941016&CFTOKEN=8596a039c3aeb875-7308FB9E-B57C-14DC-93AC7BE86DDE0B19&jsessionid=84309cd1da8989c103402e3411241a543a6c> (accessed February 28, 2012)
7. Kaye S, Darke S. The diversion and misuse of pharmaceutical stimulants: what do we know and why should we care? *Addiction.* 2012 Mar;107(3):467-77.

8 APPENDICES

8.1 APPENDIX A. ADVERSE EVENT REPORTING SYSTEM (AERS)

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

8.2 APPENDIX B. AERS CASE NUMBERS, AERS ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS OF TOPIRAMATE WITHOUT PHENTERMINE

ISR#	Case#	Manufacturer Control #
4797146	5906460	US-JNJFOC-20050405596
6327621	7102802	ADR15082009
3796591	3711447	NSADSS2001020773
3853307	3753546	CTU 159211
5819483	6707585	US-JNJFOC-20080704143
4458574	4221938	US-JNJFOC-20031000156
5028405	6066958	US-JNJFOC-20060602094
4424378	4139389	US-JNJFOC-20040404968
4745077	5843497	US-JNJFOC-20050702206
5318107	6305782	US-JNJFOC-20070406549
5568102	6510291	US-JNJFOC-20071204130
5671950	6374613	US-JNJFOC-20070705400
7729382	8120827	US-JNJFOC-20110812807
		US-MYLANLABS-
6355156	7114246	2009S1015511
3480979	3451975	PRIUSA2000002854
4357256	4142147	US-JNJFOC-20040405588
4744268	5861202	CTU 255982
4820796	5917676	US-JNJFOC-20051005393
5098223	6023998	US-JNJFOC-20060400886
5767080	6663409	US-JNJFOC-20080601241
6955688	7566467	US-WATSON-2010-11414
7941264	8264013	US-JNJFOC-20111109017

8.3 APPENDIX C. AERS CASE NUMBERS, AERS ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS OF PHENTERMINE AND TOPIRAMATE CONCOMITANTLY

ISR # Case # Manufacturer Control #	Age Sex Weight	Reported Suspect Medication(s)	Adverse Event(s)
6867049	57 yo	Asenapine (Saphris)	Hypoaesthesia oral, Parasthesia oral
7395898	Female		
2010SP006606	Unk		
6890997	46 yo	Atorvastatin (Lipitor)	Alopecia, Nausea, Wrong technique in drug usage process, Crying
7514953	Female	Loratidine (Claritin)	
US-PFIZER INC-2009173516	64 kg		
6960907	57 yo	Estradiol (Estring)	Vulvovaginal mycotic infection
7569752	Female		
US-PFIZER INC-2010106115	72 kg		
7201815	39 yo	Sodium oxybate (Xyrem)	Nerve compression, Intervertebral disc protrusion, Condition aggravated
7754934	Female		
JPI-P-013130	100 kg		
7406482	40 yo	Phentermine	Abnormal behaviour
7908242	Female	Topiramate (if prescribed)	
CTU 449592	86 kg		
7487536	49	Asenapine (Saphris)	Oral discomfort, Stomatitis, Pain
7821412	Female		
2010SP056159	Unk		
7523575	20	Levonorgestrel (Plan B)	Hot flush, Abdominal discomfort, Pelvic pain
7963837	Female		
US-TEVA-283536USA	82 kg		
7974391	36	Drospirenone/Ethinyl estradiol/Levomefolate (Beyaz)	Hypomenorrhoea
8286517	Female		
US-BAYER-2011-115923	Unk		

8.4 APPENDIX D



RCM
2011-1851Phentermir

8.5 APPENDIX E



RCM 2010-15 Qnexa
AERS Review Apr201

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/s/

SELENA D READY
03/14/2012

SARITA D BOYD
03/14/2012

CAROLYN J TABAK
03/15/2012

LANH GREEN
03/15/2012

ALLEN D BRINKER
03/15/2012

LINDA J SCARAZZINI
03/15/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 15, 2012

TO: Pooja Dharia, Pharm.D., Regulatory Project Manager
Mary Roberts, M.D., Medical Officer
Eric Colman, M.D., Deputy Director
Division of Metabolism and Endocrinology Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Team Leader, Good Clinical Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Tejashri Purohit-Sheth, M.D.
Branch Chief, Good Clinical Practice Assessment Branch
Acting Division Director, Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 22580

APPLICANT: Vivus, Inc.
DRUG: QNEXA® (Phentermine/Topiramate)
NME: No
REVIEW PRIORITY: Priority - Class 2 Resubmission

INDICATION: For the treatment of obesity, including weight loss and maintenance of weight loss, used in conjunction with diet and exercise

CONSULTATION REQUEST DATE: December 1, 2011
DIVISION ACTION GOAL DATE: April 17, 2012
PDUFA DATE: April 17, 2012

I. BACKGROUND:

The Applicant seeks approval of QNEXA® (VI-0521, phentermine/topiramate), for the indication of treatment of obesity, including weight loss and maintenance of weight loss for obese patients (body mass index [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). VIVUS, Inc. originally submitted NDA 22-580, a 505(b)(2) application for QNEXA® a combination of phentermine and topiramate (PHEN/TPM), on December 28, 2009; however, the submission received a Complete Response letter that included the recommendation that the Applicant submit additional data to address the Agency's concerns with cardiovascular toxicity. In the current resubmission the Applicant has provided additional data related to the long-term use of PHEN/TPM in Study OB-303, and the associated extension Study OB-305, to support the efficacy and safety of PHEN/TPM for the treatment of obesity, including weight loss and maintenance of weight loss when used in conjunction with diet and exercise.

Phentermine was initially approved in May 1959 as an appetite suppressant and is currently marketed as a generic and under various brand names such as Adipex-P. Because phentermine is a sympathomimetic amine is it classified as Schedule IV. Topiramate was initially approved in December 1996 as an anticonvulsant. The mechanism of action by which topiramate contributes to weight loss is unknown.

The protocols inspected for this NDA resubmission include:

1. Protocol OB-303, entitled "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Safety and Efficacy of VI-0521 in the Treatment of Obesity in Adults With Obesity-Related Co-Morbid Conditions"

Study OB-303 was a Phase III randomized, double-blind, multicenter, parallel-group, placebo-controlled study to evaluate the efficacy and safety of two maintenance doses of VI-0521 to treat obesity in adult subjects with obesity-related co-morbid conditions. The total duration of the study was 58-weeks, including 3 treatment periods (a two week screening period, a four week titration period, and a 52 week treatment period). Once determined to be eligible during the screening period, subjects were randomized to treatment in a 2:1:2 ratio: placebo, VI-0521 (PHEN/TPM) 7.5/46 mg, or VI-0521 (PHEN/TPM) 15/92 mg. The study was conducted at 93 clinical investigator sites in the United States. A total of 2487 subjects were randomized into the trial. Subjects were enrolled in the study from November 1, 2007 through June 30, 2009 (Date of final study report: November 18, 2009). (b) (4) was contracted by the sponsor to conduct site monitoring activities and to manage adverse event collection and review. Serious adverse event collection and review was performed by (b) (4) (b) (4)

The primary efficacy endpoint for this study was a co-primary endpoint that consisted of the percent weight loss at Week 56 and the percent of subjects with at least 5% weight loss at Week 56. Safety assessments included adverse events, clinical

- laboratory evaluations, Patient Health Questionnaire (9-item) (PHQ-9) assessment of depression, Columbia Suicide Severity Rating Scale (C-SSRS) assessment of suicidal behavior and suicidal ideation, vital signs, physical examinations, and electrocardiograms (ECGs).
2. Protocol OB-305, entitled “A Phase 3, Double-Blind, Placebo-Controlled, Multicenter Extension Study (From Study OB-303) to Determine the Safety and Efficacy of VI-0521 for the Long-Term Treatment of Obesity in Adults With Obesity-Related Co-Morbid Conditions”

Study OB-305 was a double-blind, placebo-controlled, 1-year extension to Study OB-303 to collect additional long-term safety and efficacy data on VI-0521 during a second year of exposure. This study was designed to assess the impact of weight loss and maintenance of weight loss on metabolic and cardiovascular co-morbidities, particularly the progression to type 2 diabetes. Subjects who elected to enroll in this extension study continued on the same double-blind treatment they were on when they completed study OB-303 for up to 52 weeks of additional exposure. The study was conducted at 36 clinical investigator sites in the United States. A total of 676 subjects were enrolled into the trial. Subjects were enrolled in the study from December 16, 2008 through June 8, 2010 (Date of final study report: September 29, 2010). As for Study OB-303, (b) (4) was contracted by the sponsor to conduct site monitoring activities and to manage adverse event collection and review and serious adverse event collection and review was performed by (b) (4).

The primary efficacy endpoint for this study was a co-primary endpoint that consisted of the percent weight loss from study OB-303 baseline to Week 108 and the percentage of subjects with at least 5% weight loss from study OB-303 baseline to Week 108. As for Study OB-303, safety assessments included adverse events, clinical laboratory evaluations, Patient Health Questionnaire (9-item) (PHQ-9) assessment of depression, Columbia Suicide Severity Rating Scale (C-SSRS) assessment of suicidal behavior and suicidal ideation, vital signs, physical examinations, and electrocardiograms (ECGs).

The clinical investigator site chosen for inspection was selected because it was among one of the highest enrolling sites (6% of subject population) in these studies and because it reported one of the largest mean differences in percent body weight change (-13.7%) from baseline to week 108.

II. RESULTS (By Site)

Name of CI	Protocol # Site# Subject#	Inspection Date	Final Classification
Donald Hurley, M.D. Medical Research South 1483 Tobias Gadson Boulevard Suite 101 Charleston, SC 29407	Site #148 Protocol: OB-303 Enrolled: 77 Protocol: OB-305 Enrolled: 38	January 10 - 27, 2012	Pending (Preliminary Classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI* = Significant deviations from regulations. Data unreliable Study C119.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and/or complete review of EIR is pending.**1. Donald Hurley, M.D.**Medical Research South
1483 Tobias Gadson
Boulevard Suite 101
Charleston, SC 29407
Site #148**a) What was inspected:**

For Study OB-303, at this site, 117 subjects were screened, 77 subjects were enrolled, and 63 subjects completed the study. Twenty-five enrolled subjects' records were reviewed during the inspection for Study OB-303. For Study OB-305, at this site, 63 subjects were screened, 38 subjects were enrolled, and 34 subjects completed the study. Twenty enrolled subjects' records were reviewed during the inspection for Study OB-305. The record audit included comparison of source documentation and CRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated clinical laboratory report documentation, test article accountability, IRB approvals, and correspondence between the site and study monitors. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the sponsor to the agency in NDA 22580 for Studies OB-303 and OB-305 were compared and verified. The investigator's execution of the protocol was found to be adequate and a Form FDA 483 was not issued to the clinical investigator.

c) Assessment of data integrity:

The data provided by Dr. Hurley's site for Studies OB-303 and OB-305 that were submitted to the Agency in support of NDA 22580 appear to be reliable and acceptable for use in support to the pending application.

Note: A complete review of the EIR was not available at the time this CIS was written. The general observations described above are based on preliminary communications provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon final review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

One clinical investigator site was inspected in support of this application resubmission. Based on the review of preliminary inspectional findings for Dr. Hurley, Study OB-303 and Study OB-305 data collected by this site appear reliable in support of NDA 22580. The preliminary classification for the inspection of Dr. Hurley is No Action Indicated (NAI).

Note: All observations noted above are based on preliminary communications with the field investigator for this inspection; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR for this inspection.

{ See appended electronic signature page }

Jean Mulinde, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Lauren Iacono-Connors, Ph.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{ See appended electronic signature page }

Tejashri Purohit-Sheth, M.D.
Branch Chief, Good Clinical Practice Assessment Branch
Acting Division Director, Division of Good Clinical Practice
Compliance
Office of Scientific Investigations

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/s/

JEAN M MULINDE

02/15/2012

TEJASHRI S PUROHIT-SHETH

02/15/2012

LAUREN C IACONO-CONNORS

02/15/2012

**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**

Label and Labeling Review

Date: February 10, 2012

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Deputy Director Kellie Taylor, PharmD, MPH
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name & Strength(s): Qnexa (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

Application Type/Number: NDA 022580

Applicant/sponsor: Vivus, Inc

OSE RCM #: 2011-4184

*** This document contains proprietary and confidential information that should not be released to the public.***


1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Qnexa (Phentermine and Topiramate) Controlled Release Capsules, for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The revised carton labeling and container labels were submitted by the Applicant on December 21, 2011 in response to our recommendations made November 17, 2011 (OSE Review # 2010-129).

1.2 PRODUCT INFORMATION

- Active Ingredient: Phentermine and Topiramate
- Indication of Use: Adjunct to diet and exercise to aid in weight loss in obese patients or overweight patients
- Route of Administration: Oral
- Dosage Form: Extended-release Capsules
- Strength: 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg
- Dose and Frequency of Administration: The recommended starting dose is 3.75 mg/23 mg by mouth once daily. The dose can be titrated up to a maximum dose of 15 mg/92 mg by mouth once daily.
- How Supplied: Bottles containing 30 capsules (b) (4)

- Storage: Store at room temperature (15°C to 25°C; 59°F to 77°F)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 21, 2011 (See Appendix A)

(b) (4)


¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling introduce vulnerability that can lead to medication errors because the strength and dispense with medication guide lack prominence (b) (4)

. We recommend the following:

- A. General Comments (All container labels and carton labeling)
 - 1. Ensure the size of the established name is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
 - 2. Revise the established name from ‘phentermine/topiramate’ to ‘Phentermine and Topiramate’.
 - 3. Revise the dosage form to read “Extended-release Capsules.”
- B. Container Label (All Strengths)
 - 1. Minimize the prominence of the ‘Q’ graphic. As currently presented, the ‘Q’ graphic competes in prominence with the other information listed such as the product name and strength.

(b) (4)

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

REFERENCE

OSE Review # 2011-129 dated June 1, 2010. *Label and Labeling Review for Qnexa (Phentermine and Topiramate) Capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg.* Crandall, A., Safety Evaluator Division of Medication Error Prevention

and Analysis, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration.

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LISSA C OWENS
02/10/2012

CARLOS M MENA-GRILLASCA
02/10/2012

KELLIE A TAYLOR
02/10/2012

CAROL A HOLQUIST
02/10/2012

CONSULTATION REVIEW

NDA 22580

Submission Date: 10/17/2011 (Class 2 Resubmission)

Drug: Qnexa® (phentermine + topiramate), Extended release capsules

Sponsor: Vivus, Inc

Indication: Obesity (Combination centrally acting appetite suppressant)

Request for consultation from: Pooja Dharia, Pharm. D., Division of Metabolism and Endocrinology Products, CDER

Date of the request: November 1, 2011

Subject of consultation: An updated review of the AERS database for adverse pregnancy outcomes such as congenital anomalies associated with the use of topiramate.

Reviewer: Sonia Tabacova, MD, Ph.D.

Division: Psychiatry Products

Review date: January 18, 2011

Background: This review is an update of our previous consultation review on adverse fetal/neonatal events reported to FDA's AERS in association with topiramate and phentermine gestational exposures (S. Tabacova, May 26, 2010), which covered adverse events reported over the period 1997- 2009, incl. The current review covers the reports of adverse neonatal events associated with topiramate gestational exposures submitted in 2010 and 2011.

A total of 52 spontaneous reports of adverse neonatal events associated with topiramate administration as a monotherapy to pregnant women were retrieved from FDA's Adverse Event Reporting System (AERS) by Dr. Ana Szarfman. Out of these, 20 reports (16 duplicates and 4 irrelevant - exposures not prenatal) were excluded from further review. The remaining 28 reports (containing a total of 32 cases) are the subject of this review. All these are cases of congenital malformations.

Reporting sources: Out of the reviewed 28 reports, 13 originated in the U.S. and 15 were from other countries (UK, Sweden, Norway, Switzerland, Austria, Australia). Nearly a half of all reports (13 of 28) were from literature sources. Most of the reports (18 of 28) were from health professionals which supports their credibility.

Reporting period: All 28 reports (containing 32 cases) were submitted in 2010 and 2011. Information about adverse events' date of occurrence was available in 20 reports; the majority (13 of 20) took place from 2008 through 2011, incl.; the remaining 7 occurred in or before 2007, but were reported in 2010-2011.

Adverse Events' Dates

Year	Reports (n=20)*
2010, 2011	7
2008, 2009	6
2006, 2007	1
Before 2006	6

*N reports or cases with information on indication available

Indication: Information about topiramate indication was available in 17 of 28 reports. In 82% of these (14 of 17) the drug was used for treatment of maternal epilepsy in pregnancy; in only 2 cases the indication was migraine, and in 1 case topiramate was

prescribed as a mood stabilizer. No concurrent maternal diseases were reported. Thus, in the majority of cases there was uniformity in the maternal health background.

Indication

	Reports (n=17)*	Cases (n=21)*
Epilepsy	14	18
Migraine	2	2
Mood stabilizing	1	1

*N reports or cases with information on indication available

Administration and doses:

Topiramate dose was reported in 14 cases. In about a half of these (6 of 14), the daily doses were less or equal to 100 mg/day; >100 to 200 mg/day in 7 cases, and >200 mg/day in just 1 case.

Topiramate Dose, mg/day

	Reports (n=14)*	Cases (n=14)*
50	1	1
75	1	1
100	4	4
150	2	2
200	5	5
> 200	1	1

*N reports or cases with information on indication available

Information about the timing and duration of topiramate exposure in pregnancy was available in 14 reports/cases. In all of these the exposure involved the 1st trimester of pregnancy (the period of major organogenesis), and in half of them (7 of 14) topiramate administration continued throughout the entire duration of pregnancy. Thus, in all cases for which information was available, topiramate maternal exposure involved the most vulnerable period of the embryo/fetal development, the 1st trimester of gestation.

No concomitant medication with other drugs was reported.

Maternal characteristics were poorly reported; i.e., maternal age was reported in less than 30% of the cases (9 of 32); the available information shows that the prevailing maternal age was between 20 and 30 years (about 67% of women, or 6 of 9) and between 30 and 40 years (about 33% of women). Information about parity was available in single reports. Alcohol consumption (moderate) was reported in 2 cases; smoking and recreational drug use was not reported.

Pregnancy outcome: All of the outcomes were live births; twin births were reported in 2 cases. C sections were reported in 5 cases. Gestational age at birth was reported in about a third of the reports (9 of 28), including 8 term- and 1 preterm births.

Neonatal gender (reported in 20 reports/cases) was 70% males (14 of 20) and 30% females (6 of 20). Birth weight data was available in 9 reports/cases; low birth weight was seen in 2 of these.

Adverse developmental events

Congenital malformations were reported in all of the reviewed AE reports and were exclusively the reason for adverse event reporting in association with topiramate use in pregnancy (see the following table).

Congenital malformations' spectrum and reporting frequency

Type of malformation	N cases reported*	Per cent of all reported cases** (N=32)
Oral clefts	20	62.5
- <i>Cleft lip and palate</i>	8	
- <i>Cleft lip</i>	7	
- <i>Cleft palate</i>	1	
- <i>Cleft mandible</i>	1	
- <i>Not specified</i>	3	
Hypospadias	5	15.6
Cardiac atrial or ventricular septal defect	3	9.4
CNS	2	6.2
- <i>Microcephaly</i>	1	
- <i>Microphthalmia</i>	1	
Other	4	12.5
- <i>Congenital cystic kidney disease</i>	1	
- <i>Club foot</i>	1	
- <i>Spinal malformation, not specified</i>	1	
- <i>Dacryostenosis</i>	1	
Congenital malformation, not specified	2	6.2

* N of cases adds up to more than 32 due to cases of multiple malformations

**Total percentage adds up to more than 100% due to cases of multiple malformations

The reporting frequency of oral clefts overwhelmingly dominated over all other types of congenital malformations reported to FDA during 2010-11 and accounted for over two thirds (62.5%) of all malformations reported. This is in agreement with and reinforces our previous observation about the predominant reporting frequency of oral clefts relative to other malformations in association with prenatal topiramate exposure for the period up to 2009 (see S. Tabacova, Consultation review to NDA 22580, May 26, 2010). This malformation pattern is similar to the types of malformations seen in topiramate developmental toxicity studies in experimental animal species: "Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal 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) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD=400 mg/day) on a mg/m basis" (*From Topiramate labeling, under "Pregnancy"*).

Next in order by a much lower reporting frequency are hypospadias, cardiac septal defects (in full term neonates) and CNS malformations (15%, 9% and 6% of all malformation cases, respectively). It is of note that these classes of malformations were also reported, in a similar order, for the period up to 2009.

Multiple malformations involving combinations of the above defects were reported in about 15% of the cases (5 of 32), as shown in the next table.

Multiple malformations

Description	N	Note
Cleft lip and hypospadias	1	
Cleft lip, atrial septal defect and hypertelorism	1	Possibly genetic: Maternal history of hypertelorism, low intelligence and previous elective abortion due to trisomy
Cleft mandible, microphthalmia and cardiovascular defect	1	
Microcephaly and dacryostenosis (tear duct stenosis)	1	
Club foot, skin hemangioma	1	

Topiramate gestational exposure – time, duration and dose

In all congenital malformation cases, topiramate gestational exposure involved the 1st trimester of pregnancy, the period of organogenesis, most vulnerable to prenatal insults. Topiramate dose (in the reported dose range of 50 - >200 mg/day) did not appear to affect the type of AEs or the rate of their reporting, as shown below.

Topiramate dose (mg/day)

Type of malformation	N cases with dose information available/ N total:	Dose, mg/day		
		100 or less	200	>200
Oral clefts	8/20	4	3	1
Hypospadias	2/5		2	
Cardiac atrial or ventricular septal defect	2/3	1	1	
CNS	2/2	2		

Confounding factors:

- No concomitant drug use was reported.
- Maternal demographic characteristics (age, gravidity, parity) were reported in insufficient number of reports to allow for a meaningful interpretation.
- Alcohol consumption (moderate, less than 5 drinks per week) was reported in 2 cases. The types of malformations reported in these particular cases (oral clefts) were not different from the rest of the reported cases. Oral clefts have not been associated with fetal alcohol syndrome in humans.
- Family history of birth defects was reported in 2 cases (6% of all cases). These included 1 case of multiple malformations (cleft lip, atrial septal defect, hypertelorism) with maternal history of hypertelorism, low intelligence and 1 induced abortion for trisomy, and another case of cleft lip and palate with paternal history of oral cleft (but genetic testing was normal).

Conclusions:

- The adverse events reported to FDA in 2010 and 2011 in association with prenatal exposures to topiramate are exclusively congenital malformations. The reporting frequency of oral clefts overwhelmingly dominated over all other types of congenital malformations reported to FDA during the same period, accounting for over two thirds

(62.5%) of all malformations reported. This is consistent with and reinforces our previous observation about the predominant reporting frequency of oral clefts relative to other malformations in association with prenatal topiramate exposure for the period up to 2009 (S. Tabacova, Consultation Review NDA 22580, May 26, 2010).

- The type of reported congenital malformations is similar to that seen in experimental animals prenatally exposed to topiramate which indicates that the association of the reported malformations in humans with maternal exposure to topiramate during gestation is plausible.

- Our conclusion that the reported major malformations, and particularly oral clefts are associated with maternal exposure to topiramate during gestation is consistent with literature data of recently published observational and analytical epidemiological studies based on North American Pregnancy Registry and UK Epilepsy and Pregnancy Register (see below).

This conclusion is further supported by:

- The use of topiramate as a monotherapy in the reported malformation cases;
- The time and duration of the prenatal topiramate exposure, involving in all cases the 1st trimester of gestation, the period of major organogenesis, most susceptible to induction of malformations.

Although the findings of this review are not to be interpreted as a proof of a *causal* relationship to topiramate exposure since they are based on spontaneous AE reports, there is no control group, and it is not possible to determine the incidence of the adverse events (no denominator), our conclusion that the reported major malformations, and particularly oral clefts are associated with maternal exposure to topiramate during gestation is consistent with recently published epidemiological studies that provide a stronger evidence to support a causal relationship. Thus, a significant increase in the prevalence of major malformations in women exposed to topiramate monotherapy during the 1st trimester of pregnancy [3.8% (11/289) in comparison to 1.3% (5/372) in unexposed controls, relative risk of 2.8 (95% CI: 1.0 – 8.1)] was found in an analytical epidemiological study based on the North American Pregnancy Registry; the prevalence of isolated cleft lip was 10-fold higher than the expected prevalence of this malformation (Hernandez-Diaz S, Mittendorf R, Holmes L, Comparative safety of topiramate in pregnancy. *Pharmacoepidemiol. Drug Safety*, 2010; 19: abstr 290 (S 124). Major congenital malformation rate of 7.1% was found in women on topiramate in pregnancy in a 15-year prospective observational study (1996 -2009) based on the UK Epilepsy and Pregnancy Register; the risk of major congenital malformations was significantly higher in women on antiepileptic drugs during pregnancy in comparison to those on no treatment (Kennedy F et al: Malformation risks of antiepileptic drugs in pregnancy: An update from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psych*, 2010, 81 (11):E18).

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/s/

SONIA A TABACOVA
01/26/2012

AISAR H ATRAKCHI
01/26/2012

THOMAS P LAUGHREN
01/27/2012



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

Date: January 20, 2012

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II, OND, CDER

Through: Tarek A. Hammad, MD, PhD, MSc, MS, Deputy Director
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Diane K Wysowski, PhD, MPH, Team Leader
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: Addendum to Review of sponsor's Qnexa teratogenicity
report entitled "Clinical review of topiramate and PHEN/TPM
teratogenic potential" dated September 27, 2011

Drug Name(s): Qnexa (phentermine & topiramate)

Submission Number:

Application Type/Number: NDA 22580

Applicant/sponsor: Vivus

OSE RCM #: 2011-4184

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EXECUTIVE SUMMARY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP) in preparation for the Advisory Committee meeting on February 22, 2012, the Qnexa teratogenicity report entitled “Clinical review of topiramate and PHEN/TPM teratogenic potential” dated September 27, 2011, and three abstracts/posters that were cited in this report were reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

In summary, each of the three studies has limitations, but with different directions of bias and significance. All three investigated the effect of TPM exposure during the first trimester of pregnancy on live birth infants. The fetal outcomes that ended in abortion (spontaneous or induced), or stillbirth could not be assessed. Overall, the Slone/CDC study provided more reliable risk estimates of oral clefts (OCs) associated with TPM exposure during the first trimester of pregnancy compared to the other two studies. The risks of OCs and major congenital malformations (MCMs) were probably underestimated in the Wolters Kluwer study because most of the study limitations would bias the results towards no association between TPM exposure and risk of OCs. The sponsor’s comment that the Denmark study confirms an absence of a signal for an increased prevalence of MCMs with topiramate exposure is not supported because of the limited statistical power of the Denmark study.

1 BACKGROUND/HISTORY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), the Qnexa teratogenicity report entitled “Clinical review of topiramate and PHEN/TPM teratogenic potential” dated September 27, 2011, and three abstracts/posters that were cited in this report were reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

Qnexa is a combination of two marketed products, phentermine and topiramate (TPM), for which the applicant is seeking approval for the treatment of obesity and overweight. If approved, Qnexa will be available in three fixed-dose combinations of phentermine/topiramate: 3.75mg/23mg, 7.5mg/46mg, and 15mg/92mg. Recent reports based on registry data from the U.S. and the U.K. have suggested that infants exposed to

topiramate (TPM) in utero have an increased risk of oral clefts (OCs) and major congenital malformations (MCMs).^{1,2,3}

This review will comment on the methodologies, study results, and strengths and limitations of the three studies. DEPI will also provide possible reasons for the differences in results between the Slone/CDC and the Wolters Kluwer studies based on limited information available from the abstracts, posters, and the Qnexa teratogenicity report. Finally we will comment on the sponsor's statement that the Denmark study confirms an absence of a signal for increased prevalence of MCMs with TPM exposure.

2 REVIEW MATERIALS

Materials that were included in this review are:

- A published cohort study by Molgaard-Nielsen (referred throughout this review as the Denmark Study)⁴;
- A study abstract by Margulis et al. that was presented at the 27th ICPE meeting (referred throughout this review as the Slone/CDC study)³;
- An abstract and poster of a part of a study funded by the sponsor using the Wolters Kluwer Pharma Solutions data by Green et al. that was presented at the 136th Annual meeting of the American Neurological Association (referred throughout this review as the Wolters Kluwer study)⁵;
- An abstract and poster of a different part of the study funded by the sponsor using the Wolters Kluwer Pharma Solutions data by Pack et al. that was presented at the 29th International Epilepsy Congress (referred throughout this review as the Wolters Kluwer study)⁶; and
- The Qnexa teratogenicity report entitled “Clinical review of topiramate and PHEN/TPM teratogenic potential” dated September 27, 2011.

3 RESULTS OF REVIEW

3.1 STUDY SYNOPSIS

3.1.1 Slone/CDC Study

Data from two case-control surveillance programs in North America, the Slone Epidemiology Center Birth Defects Study (BDS, 1997-2009) and the Center for Disease Control's National Birth Defects Prevention Study (NBDPS, 1996-2007) were analyzed to examine the association between the use of TPM in pregnancy and the risk of cleft lip with or without cleft palate and isolated cleft palate. Logistic regression models were used to compare first trimester use of TPM monotherapy vs. no use of antiepileptics between cases and non-malformed controls matched on year and region of birth. The median daily dose of TPM was 100 mg for both cases and controls (range: 25-150 mg). The odds ratio (OR) for MCMs was 1.22 (95% CI, 0.19-13.01) in the Slone data and 0.92 (95% CI, 0.26-4.06) in the CDC data; for cleft lip with or without cleft palate, the OR was 10.13 (95% CI, 1.09-129.21) in the Slone data and 3.63 (95% CI, 0.66-20.00) in the CDC data. The pooled OR was 1.01 (95% CI, 0.37-3.22) for MCM and 5.36 (95% CI, 1.49-20.07) for cleft lip with or without cleft palate. There was no case of isolated cleft palate in TPM-exposed pregnancies. The study concluded that first-trimester use of TPM monotherapy may be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate or overall MCMs.

3.1.2 Wolters Kluwer Study

A retrospective cohort study sponsored by Vivus used data from Wolters Kluwer Pharma Solutions Source LX Patient longitudinal datasets (January 2003 – December 2010) from the United States to examine the risk of MCMs, including OCs, among infants exposed to TPM in utero anytime during pregnancy (n=910) and during the first trimester only (n=870). Five control cohorts were comprised of:

- 1) Women exposed to other antiepileptic drugs (AEDs) during the first trimester of pregnancy (n=3,615);
- 2) Women with a diagnosis of epilepsy but without TPM exposure (n=2,607);
- 3) Women with a diagnosis of migraine but no diagnosis of epilepsy and not treated during pregnancy with acute and preventive migraine drugs (n=26,865);

4) Women with a diagnosis of migraine but no diagnosis of epilepsy and treated during pregnancy with acute and preventive migraine drugs (n=2,526); and

5) Women with a diagnosis of diabetes other than gestational (n=13,063).

The relative risks (RR) of MCMs were:

- 1.33 (95% CI, 0.92-1.90) for TPM vs. other AEDs
- 0.98 (95% CI, 0.68-1.41) for TPM vs. the epilepsy control group
- 1.12 (95% CI, 0.81-1.55) for TPM vs. migraine control group
- 0.99 (95% CI, 0.68-1.42) for TPM vs. treated migraine control group
- 0.65 (95% CI, 0.47-0.89) for TPM vs. the diabetes control group

The RRs of OCs were:

- 1.39 (95% CI, 0.28-6.85) for TPM vs. other AEDs
- 0.88 (95% CI, 0.18-4.21) for TPM vs. the epilepsy control group
- 1.47 (95% CI, 0.36-6.06) for TPM vs. migraine control group
- 0.95 (95% CI, 0.19-4.68) for TPM vs. treated migraine control group
- and 0.88 (95% CI, 0.21-3.67) for TPM vs. the diabetes control group

This study concluded that there was no significantly increased risk of OCs or MCMs associated with TPM exposure during the first trimester of pregnancy or anytime during pregnancy.

3.1.3 Denmark Study

A population-based cohort study in Denmark examined the association between fetal exposure to newer-generation AEDs (lamotrigine, oxcarbazepine, topiramate, gabapentin, levetiracetam) during the first trimester of pregnancy and the risk of major birth defects from January 1, 1996, through September 30, 2008. A major birth defect was diagnosed in 5 out of 108 infants exposed to TPM compared with 19,911 out of 836,263 infants with no exposure to any of the newer-generation AEDs. The adjusted prevalence odds ratio of major birth defect was 1.44 (95% CI, 0.58-3.58) for TPM exposure vs. unexposed to any newer-generation AEDs. The study concluded that first-trimester exposure to newer-generation AEDs compared with no exposure was not associated with an increased risk of major birth defects.

3.2 STUDY ELEMENTS & DEPI COMMENTS

3.2.1 Study Objectives

3.2.1.1 Study Objectives:

Slone/CDC study:

- To evaluate the association between the use of TPM in the first trimester of pregnancy and the risk of cleft lip with or without cleft palate and isolated cleft palate

Wolters Kluwer study:

- To examine the risk of MCMs and OCs, among infants exposed to TPM in utero compared to controls

Denmark study:

- To study the association between fetal exposure to newer-generation antiepileptic drugs (AEDs) during the first trimester of pregnancy and the risk of major birth defects

3.2.1.2 Reviewer Comments:

Both the Slone/CDC and the Wolters Kluwer studies examined the effect of TPM exposure during pregnancy, while the Denmark study examined the combined effect of newer-generation AEDs. The Denmark study was not powered to examine the individual effect of TPM exposure. The primary study outcome for both the Slone/CDC and the Wolters Kluwer study was OCs. However, the primary outcome for the Denmark study was MCMs.

3.2.2 Study Design

3.2.2.1 Study Design:

Slone/CDC study:

- A pooled case-control study (consisting of two separate case-control studies, one from the Slone Epidemiology Center and the other from CDC)

Wolters Kluwer study:

- A retrospective cohort study

Denmark study:

- A retrospective cohort study

3.2.2.2 Reviewer Comments:

An observational cohort study can be advantageous over a case-control study when it comes to recall bias which is often associated with case-control studies. Since controls were non-malformed infants in the Slone/CDC study, a differential recall bias may exist between cases and controls in reporting drug exposure, including TPM exposure, during the first trimester of pregnancy.

Since the study outcome of OCs are rare and the exposure is limited, a case-control study can be a very efficient study design. A cohort study, on the other hand, may suffer from inadequate sample size and study power, which is unfortunately the case for the Wolters Kluwer study and the Demark study.

3.2.3 Data Sources

3.2.3.1 Data Sources:

Slone/CDC study:

- The Slone Epidemiology Center Birth Defects Study (BDS), 1997-2009
- The Center for Disease Control's National Birth Defects Prevention Study (NBDPS), 1996-2007

The Slone Epidemiology Center is a public health research organization focusing on studying the possible health effects of medications in adults and children. The Birth Defects Study (BDS) is a case-control birth defects study spanning over 25 years that assesses the risks of birth defects in relation to medications taken during pregnancy. The database currently has information on over 32,700 mother-child pairs.

The National Birth Defects Prevention Study (NBDPS) is a population-based, case-control study examining the risk factors and potential causes of birth defects with data collection since 1997. The Centers for Disease Control and Prevention (CDC)

coordinated the NBDPS, which is a collaborated study by ten study centers (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Women whose babies have birth defects were invited to participate in the study. Women whose babies do not have birth defects were selected randomly from women who gave birth in the same area during the same year. Phone interviews are conducted to collect information on past pregnancies, health and diet, prescription and non-prescription drugs, work and hobbies, lifestyle, and father's work and lifestyle. Genetic data are collected from cheek cells from mothers, fathers, and babies.

Wolters Kluwer study:

- The Wolters Kluwer Pharma Solutions Source Lx Patient longitudinal data, January 2003 – December 2010

The Wolters Kluwer Source Lx Patient database is a longitudinal patient data source which captures adjudicated prescription and medical claims across the United States from commercial plans, cash payments, Medicare Part D plans, and Medicaid claims. Source Lx Patient data contains information on patient age and gender, prescriber specialty and geography, prescriptions, diagnoses, and procedures. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics and outpatient facilities, and 80,000 physician practices. Patients in Source Lx are distributed proportionally to the 2009 U.S. Census in the Northeast and Southern Census regions. However, the population is underrepresented in the Midwest and overrepresented in the West.

Denmark study:

- The Medical Birth Registry in Denmark, January 1, 1996 – September 30, 2008
- The Registry of Medicinal Product Statistics in Denmark (time frame not provided)
- The National Patient Registry in Denmark, January 1, 1996 – March 31, 2009

A study cohort of all live births from January 1, 1996, through September 30, 2008 was constructed using the Medical Birth Registry. The Medical Birth Registry contains records on all Danish births, which include the personal identification numbers

of the parents and the newborn, date of birth, indication of single vs. multiple births, gestational age, vital status, and other physical characteristics of the newborn.

Exposure to AEDs was obtained from the Registry of Medicinal Product Statistics, which contains patient-level data on all prescriptions dispensed at Danish pharmacies since 1994. The information includes the personal identification number of the patient, drug names, number of units of the product sold, and the number of defined daily doses.

Cases of birth defects were identified through the National Patient Registry from January 1, 1996, through March 31, 2009. This registry contains individual patient-level data on all inpatients and outpatients encountered at hospitals and ambulatory care, including the personal identification number (that was used to link to the Medical Birth Registry), dates of admission and discharge, and diagnoses classified according to the International Classification System of Diseases.

3.2.3.2 Reviewer Comments:

The BDS and NBDPS databases that were used in the Slone/CDC study were based on patient self-reported data collected from surveys and the diagnostic information from the medical records. Patient participation was voluntary and the study samples are not nationally representative. It is unknown whether study participants are different from non-participants with regard to TPM exposure and types of birth defects.

Although the Wolters Kluwer Source Lx Patient database provides a large sample of patients who are demographically representative of the U.S. health care population, those patients are not nationally representative. The study outcomes were not validated by medical records. The prescription dispensing data may have over-estimated the rates of exposure by assuming that all individuals were 100% compliant with the prescriptions and used the medication until the last dose. As a result, a misclassification bias in exposure might have been introduced. Some confounding factors, such as family history of OCs, alcohol and tobacco use, substance abuse, and other important lifestyle risk factors, were not available to be adjusted for in this claims data analysis.

The Danish Medical Birth Registry and the National Patient Registry contain patient-level data on all inpatients and outpatients encountered in ambulatory care in

Denmark. However, data from the primary care setting were not included. According to the study's investigators, the fact that the cases were limited to those who were diagnosed at hospitals and in ambulatory care may have resulted in an under-estimation of the prevalence rate of major birth defects.

3.2.4 Study Population

3.2.4.1 Study Population:

Slone/CDC study:

- The base study population consisted of women who participated in the BDS and NBDPS studies.
- The cases were women whose babies had cleft lip with or without cleft palate, or isolated cleft palate, or MCMs.
- The controls were women whose babies were non-malformed.

Wolters Kluwer study:

- The base study population consisted of all women with medical claims relating to pregnancy and had medical data over the 13 months prior to birth and had linked infant data available for 12 months after birth.
- The TPM-exposed cohort included mother-baby pairs who were exposed to TPM at any dose, for any duration, and for any indication during pregnancy.
- The other AED control cohort included mother-baby pairs who were exposed to other AEDs for any indication during pregnancy.
- The epilepsy control cohort included women with a diagnosis of epilepsy who had no TPM exposure during pregnancy.
- The migraine control cohort included women with a diagnosis of migraine, but no epilepsy, no treatment during pregnancy with acute and preventive migraine drugs (APMD), and no TPM exposure during pregnancy.
- The migraine treated during pregnancy control cohort included women with a diagnosis of migraine treated during pregnancy with APMD, but no epilepsy and no TPM exposure during pregnancy.

- The diabetes control cohort included women with a diagnosis of type 1 or type 2 diabetes who had no TPM exposure during pregnancy and no history of epilepsy.

Denmark study:

- The base population consisted of women who had given live birth during the study time.
- The TPM-exposed cohort included women who were exposed to TPM during the first trimester of pregnancy.
- The unexposed control cohort included women who had no exposure to any newer-generation AEDs during the first trimester of pregnancy.

3.2.4.2 Reviewer Comments:

Recall bias of drug exposure, including TPM exposure, during pregnancy may exist in the Slone/CDC study since mothers in the control groups who had non-malformed babies may be less likely to recall their exposure to TPM during pregnancy compared to mothers of cases.

In the Wolters Kluwer study, multiple control cohorts were used to compare the relative risks (RRs) of MCMs and OCs associated with TPM exposure during pregnancy. Although the control cohorts of epilepsy, migraine, migraine treated during pregnancy, and diabetes were homogeneous subgroups of patients, the exposed cohort of interest, the TPM-exposed cohort is not. The TPM-exposed cohort consisted of women with TPM exposure at any dose, for any duration, and for any indication during pregnancy. Therefore, the RRs of OCs and MCMs associated with TPM exposure vs. these control cohorts are potentially confounded by the underlying conditions that was not the condition of the control cohort.

(b) (4)

The study population is appropriate in the Denmark study.

3.2.5 Exposures

3.2.5.1 Exposures:

Slone/CDC study:

- Exposure to TPM at any dose, for any duration, and for any indication during the first trimester of pregnancy

Wolters Kluwer study:

- Exposure to TPM at any dose, for any duration, and for any indication anytime during pregnancy
- Exposure to TPM at any dose, for any duration, and for any indication during the first trimester of pregnancy

Denmark study:

- Exposure to newer-generation AEDs, including TPM, at any dose, for any duration, and for any indication during the first trimester of pregnancy

3.2.5.2 Reviewer Comments:

The exposure definitions in the Slone/CDC study are appropriate. As OCs occur very early in the development of the fetus, it is important to restrict the exposure to TPM within the first trimester of pregnancy so that the time sequence, one of the criteria for the causal nature of an association, is met. Therefore, the risks in the Wolters Kluwer study were underestimated when the exposure data were anytime during the pregnancy because exposure occurred after the first trimester would not affect the development of OCs. The Qnexa teratogenicity report provide additional data for the Wolters Kluwer study on the prevalence rates of OCs and MCMs in children born to women exposed to TPM during the first trimester of pregnancy, which is more appropriate risk window for the assessment of TPM use and risk of OCs.

Another concern is that the risk attributable to TPM cannot be distinguished in the Wolters Kluwer study since the exposure was any exposure to TPM during pregnancy which included TPM monotherapy and/or polytherapy with other AEDs. In contrast, the

Slone/CDC study examined TPM monotherapy and the risk of OCs. The definition of "pregnancies" was based on the delivery date in the Wolters Kluwer study (first trimester was defined as from the earliest possible date of conception through 84 days following the latest possible date of conception, e.g., days 287 through 169 before the delivery date for singleton births at term), which may be subject to misclassification bias because of the nature of claims data. It is unclear how the researchers dealt with missing infant birth dates and ICD-9 codes for birth terms (pre-term, full-term, post-term).

The prescription dispensing data used in the Wolters Kluwer and the Denmark studies may have over-estimated the rates of exposure by assuming that all individuals were 100% compliant with the prescriptions and used the medication until the last dose. As a result, a misclassification bias in exposure might have been introduced. Another concern is that the exposure of interest in the Denmark study was newer-generation AEDs. It is unclear whether the exposure to TPM included TPM monotherapy and/or polytherapy with other AEDs. Lastly, as there were only 108 women exposed to TPM during their first trimester of pregnancy, the study power to examine the association between TPM exposure and risk of OCs and MCMs was limited.

3.2.6 Disease Outcomes of Interest

3.2.6.1 Study Outcomes:

Slone/CDC study:

- Cleft lip with or without cleft palate
- Isolated cleft palate

Wolters Kluwer study:

- MCMs
- Oral clefts

Denmark study:

- MCMs

3.2.6.2 Reviewer Comments:

In the Slone/CDC study, the study outcomes are specific types of oral clefts: cleft lip with or without cleft palate and isolated cleft palate. However, the other two studies used a general term of oral clefts and did not differentiate the cleft lip with or without cleft palate and isolated cleft palate. Since there may be differential diagnosis/ascertainment rates of cleft lip with or without cleft palate and isolated cleft palate and differential risks were observed from the Slone/CDC study (first-trimester use of TPM in monotherapy was found to be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate in the Slone/CDC study), the risk estimates in the Wolters Kluwer study and the Denmark study could be diluted by using the composite OCs as study outcome. Another concern for the Wolters Kluwer study is that the study outcomes were not validated by medical records, which could potentially bias the estimated relative risks toward the null due to potential non-differential misclassification of study outcomes.

The main outcome measure was all major birth defects in the primary analyses of the Denmark study. Subgroups of birth defects, e.g. OCs, were investigated in additional exploratory analyses. Infants with chromosomal aberrations, genetic disorders, and birth defects with known causes, such as fetal alcohol syndrome were excluded. The study outcomes were not validated in this study. However, it seems that validity of birth defect diagnoses through the national Patient Registry is high with a predictive value of 88% for birth defects overall⁷.

3.2.7 Study Covariates

3.2.7.1 Study Covariates

Potential confounders adjusted for in these three studies are listed in Table 1.

Table 1. Study covariates evaluated in each study

Potential Confounders	Slone/CDC Study *	Wolters Kluwer Study **	Denmark Study ***
Maternal age	√		√
Maternal obesity	√		
Maternal diabetes	√	√	
Folic acid intake	√		
Epilepsy	√	√	√
Migraine		√	√
Exposure to other AEDs		√	√
Maternal alcohol use	√		
Smoking	√		√
Maternal and family history of MCMs	√		
History of birth defects in siblings			√
Birth year	√		√
Mother's parity			√
Race	√		√
Geographic area	√		√
Level of mother's education			√
Level of mother's socioeconomic status			√

* In the Slone/CDC study, cases and controls were matched on birth year and region of birth. The pooled analysis additionally matched on study. Sensitivity analysis further matched, one by one, on folic acid intake, epilepsy, smoking, and other potential confounders. The results did not change meaningfully.

** In the Wolters Kluwer study, crude (unadjusted) relative risks were calculated comparing the prevalence rates of OCs and MCMs in the TPM-exposed cohort with each

comparator cohort, which include epilepsy cohort, migraine without treatment during pregnancy cohort, migraine with treatment during pregnancy cohort, and diabetes cohort.

*** In the Denmark study, the potential confounders were individually included in separate models with AED use and selected for the final adjusted regression models if they changed the prevalence odds ratios (PORs) by 10% or more. Maternal use of older-generation AEDs during the first trimester of pregnancy and maternal diagnosis of epilepsy were the only covariates that changed the PORs by 10% or more. Only these two covariates were included in the final analysis.

3.2.7.2 Reviewer Comments:

Ideally, all potential confounders should be included in multivariate analyses simultaneously to examine the independent effect of TPM exposure on OCs and MCMs. However, some data sources have incomplete or unavailable information on these study covariates. The Wolters Kluwer claims data do not contain information on many potential confounders. Even with the limited number of confounders available, the Wolters Kluwer study only calculated the crude relative risks.

The Slone/CDC study data are self-reported which may be subject to recall bias as well as reporting bias. Some patients with certain risk factors, such as smoking, alcohol abuse, and obesity may not report them. The Denmark study examined an extensive list of potential confounders and provided the adjusted relative risk of major birth defects associated with TPM exposure. However, some of the important potential confounders were not included in this study, such as, maternal diabetes, maternal obesity, folic acid intake, and maternal alcohol use.

3.2.8 Sample Size

3.2.8.1 Sample Size

Slone/CDC study:

In the Slone BDS database, 3 (0.39%) of 781 cases of cleft lip with or without cleft palate had TPM exposure during the first trimester of pregnancy compared with 2 (0.03%) of 6,935 controls. In the CDC NBDPS database, 4 (0.18%) of 2,260 cases of

cleft lip with or without cleft palate TPM exposure during the first trimester of pregnancy compared with 4 (0.05%) of 8,438 controls.

Wolters Kluwer study:

A total of 870 women were exposed to TPM during the first trimester of pregnancy.

Denmark study:

There were 108 women who had exposure to TPM during the first trimester of pregnancy.

3.2.8.2 Reviewer Comments:

None of the studies reported the *a priori* calculations of power for their analyses. In this case, the upper limit of the 95% confidence interval should provide a cap on the risk that a given study can exclude. However, estimates with wide confidence intervals are less reliable. The Denmark study acknowledged that the analyses of TPM were based on a limited number of exposures. The primary author of the Denmark study stated that “Topiramate use is rare in our cohort and the FDA warning on topiramate and clefts was published after we conducted our analyses and as such our study was not designed to evaluate this association. We only evaluated specific groups of birth defects in the context of any newer generation antiepileptic drugs and lamotrigine alone, where we had sufficient statistical power.” (Personal communication from Ditte Molgaard-Nielsen to Amy Egan on May 24, 2011)

3.2.9 Analyses

3.2.9.1 Analyses

Slone/CDC study:

Logistic regression models were used to compare first trimester use of TPM monotherapy vs. no use of AEDs between cases and controls matched on year and region of birth. Analyses were conducted separately on each database and on the pooled data, additionally matching on study. Sensitivity analyses were performed by further matching one by one on folic acid intake, epilepsy, smoking, and other potential confounders.

Wolters Kluwer study:

Crude (unadjusted) relative risks and 95% confidence intervals were calculated to compare the prevalence rates of OCs and MCMs in the TPM-exposed cohort with each comparator cohort.

Denmark study:

Logistic regression models were used to estimate the prevalence odds ratios of all MCMs with 95% confidence intervals. The odds ratios were adjusted for use of older-generation AEDs during the first trimester and maternal diagnosis of epilepsy.

3.2.9.2 Reviewer Comment:

A multivariate analysis adjusting for all study covariates simultaneously should be performed to estimate the independent effect of TPM exposure in the first trimester on OCs and MCMs. However, the Slone/CDC study adjusted for these study covariates by matching cases with controls on potential confounders, one by one, in a series of sensitivity analyses. Because of the lack of simultaneous adjustment, the reported risk estimates in this study might be affected by residual confounding. The Wolters Kluwer study only estimated crude relative risk without adjusting for potential confounders. The Denmark study evaluated the potential confounders by individually including them in separate models with AED use and selected for the final adjusted regression models if they changed the PORs by 10% or more. Maternal use of older-generation AEDs during the first trimester of pregnancy and maternal diagnosis of epilepsy were the only covariates that changed the relative risks by 10% or more and only these two covariates were included in the final analysis.

3.2.10 Study Results

3.2.10.1 Study Results

Slone/CDC study:

This study found that the median daily dose of TPM was 100 mg for both cases and controls (rang: 25-150 mg). As shown in Table 2, the odds ratio (OR) for MCM was 1.22 (95% CI, 0.19-13.01) in the Slone data and 0.92 (95% CI, 0.26-4.06) in the CDC data; for cleft lip with or without cleft palate, the OR was 10.13 (95% CI, 1.09-129.21) in

the Slone data and 3.63 (95% CI, 0.66-20.00) in the CDC data. The pooled OR was 1.01 (95% CI, 0.37-3.22) for MCM and 5.36 (95% CI, 1.49-20.07) for cleft lip with or without cleft palate. There was no case of isolated cleft palate in TPM-exposed pregnancies. The study concluded that first-trimester use of TPM monotherapy may be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate or overall MCM.

Table 2. Adjusted Odds Ratio and 95% Confidence Intervals for Topiramate vs. No AED Exposure in the First Trimester of Pregnancy by Study.

Study	Case/Control	Number of Mothers without any AED Exposure	Number of Mothers with Topiramate Exposure	Adjusted OR (95% CI)
Slone BDS	Control	6,933	2	Reference
	MCMs*	10,503	5	1.22 (0.19–13.01)
	CL/P**	778	3	10.13 (1.09–129.21)
CDC NBDPS	Control	8,434	4	Reference
	MCMs*	23,102	10	0.92 (0.26–4.06)
	CL/P**	2,256	4	3.63 (0.66–20.00)
Combined	Control	15,367	6	Reference
	MCMs*	33,605	15	1.01 (0.37–3.22)
	CL/P**	3,034	7	5.36 (1.49–20.07)

*MCMs: Major congenital malformations

**CL/P: Cleft lip with or without cleft palate

Wolters Kluwer study:

None of the relative risks (RR) of MCMs or OCs were statistically increased for the TPM-exposed cohort vs. each comparator cohort. The estimated relative risks for OCs and MCMs associated with TPM exposure anytime during pregnancy and during the first trimester of pregnancy were summarized in Tables 3 and 4, respectively. This study concluded that there was no significantly increased risk of OCs or MCMs with TPM exposure during pregnancy.

Table 3. Prevalence Rates of OCs and MCMs in Children Born to Women Exposed to TPM Anytime During Pregnancy

	n	Oral Clefts		MCMs	
		Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator	Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator
TPM	910	0.22	n/a	3.96	n/a
Other AEDs	4320	0.23	0.95 (0.21–4.33)	3.38	1.17 (0.82–1.67)
Epilepsy	2607	0.31	0.72 (0.15–3.37)	4.33	0.91 (0.63–1.32)
Migraine	26865	0.16	1.41 (0.34–5.80)	3.79	1.05 (0.75–1.45)
Migraine APMD*	3339	0.33	0.67 (0.15–3.00)	3.95	1.00 (0.70–1.44)
Diabetes	13063	0.26	0.84 (0.20–3.51)	6.58	0.60 (0.43–0.83)

* APMD: acute and preventive migraine drugs

Table 4. Prevalence Rates of OC and MCM in Children Born to Women Exposed to TPM during the First Trimester of Pregnancy

	n	Oral Clefts		MCMs	
		Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator	Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator
TPM	870	0.23	n/a	4.25	n/a
Other AEDs	3615	0.17	1.39 (0.28–6.85)	3.21	1.33 (0.92–1.90)
Epilepsy	2607	0.31	0.75 (0.16–3.52)	4.33	0.98 (0.68–1.41)
Migraine	26865	0.16	1.47 (0.36–6.06)	3.79	1.12 (0.81–1.55)
Migraine APMD*	2526	0.24	0.95 (0.19–4.68)	4.32	0.99 (0.68–1.42)
Diabetes	13063	0.26	0.88 (0.21–3.67)	6.58	0.65 (0.47–0.89)

* APMD: acute and preventive migraine drugs

Denmark study:

As shown in Table 5, the adjusted prevalence odds ratio of major birth defects is 1.44 (95% CI, 0.58-3.58) for TPM-exposed vs. unexposed to any newer-generation AEDs. The study concluded that first-trimester exposure to newer-generation AEDs compared with no exposure was not associated with an increased risk of major birth defects.

Table 5. Association between First-Trimester Exposure to Newer-Generation AEDs and Major Birth Defects

First Trimester Exposure	No. of Women	No. (%) Birth Defects	Crude POR (95% CI)	Adjusted POR (95% CI)
None	836,263	19,911 (2.4)	1.0 (Reference)	1.0 (Reference)
AED*	1532	49 (3.2)	1.35 (1.02–1.80)	0.99 (0.72–1.36)
Topiramate	108	5 (4.6)	1.99 (0.81–4.88)	1.44 (0.58–3.58)
* lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam POR=prevalence odds ratio; CI=confidence interval; AED=antiepileptic drug				

3.2.10.2 Reviewer Comment:

As discussed previously, due to limited study power, the risk estimates from the Wolters Kluwer and the Denmark studies should be considered as exploratory and interpreted with caution. Because of the lack of simultaneous adjustment, reported risk estimates from the Slone/CDC study might be affected by residual confounding.

Since the Denmark study only provided the risk estimates for major birth defects, DEPI calculated the crude prevalence odds ratio of OCs associated with TPM exposure in the first trimester of pregnancy using the data provided in the Denmark study and the results were provided in Table 6. Please note the wide 95% confidence interval which suggests the inadequate sample size.

Table 6. Estimated crude prevalence odds ratio of oral clefts associated with first-trimester TPM exposure (data source: the Denmark study)

First Trimester Exposure	Number of Women	Number of Oral Cleft	Crude POR (95% CI)
Unexposed to any newer generation AED	836263	1421	Reference
Topiramate	108	1	5.45 (0.77-38.36)

4 DISCUSSION

4.1 COMPARISON BETWEEN THE SLONE/CDC & THE WOLTERS KLUWER STUDIES

The following is a summary of our comments concerning the inconsistent findings between the Slone/CDC and the Wolters Kluwer studies.

1. Compared to the Slone/CDC study where the exposure of interest was TPM monotherapy during the first trimester of pregnancy, the Wolters Kluwer study examined the association of any TPM use anytime during pregnancy and oral clefts. As the risk window for oral clefts is primarily in the first trimester, using TPM exposure that occurred anytime during pregnancy could have diluted the risk of TPM and bias the risk estimates towards the null in the Wolters Kluwer study. All risk estimates were higher in the analyses with TPM exposure only in the first trimester of pregnancy compared to those with TPM exposure anytime during pregnancy in the Wolters Kluwer study, which showed the importance of specifying an appropriate risk window for exposure.
2. The definition of "pregnancies" was based on the delivery date in the Wolters Kluwer study, which may be subject to misclassification bias because of the nature of claims data. It is unclear how the researchers dealt with missing infant birth date and ICD-9 codes for birth terms (pre-term, full-term, post-term).
3. It is not clear how the Wolters Kluwer study defined "oral clefts". It seems that this study did not differentiate the cleft lip with or without cleft palate and isolated cleft palate. Since there may be differential diagnosis/ascertainment rates of oral clefts with or without cleft palate and isolated cleft palate and differential risks were observed in the Slone/CDC study (first-trimester use of TPM in monotherapy was found to be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate in the Slone/CDC study), the risk estimates in the Wolters Kluwer study may be diluted.
4. The risk attributable to TPM cannot be distinguished in the Wolters Kluwer study since the exposure was any exposure to TPM during pregnancy which included TPM monotherapy and polytherapy with other AEDs. In contrast, the Slone/CDC study examined the risk of OCs with TPM monotherapy.

5. It is possible that the Wolters Kluwer study have missed some exposures and outcomes since they may not have all claims for these patients, which was acknowledged in their study posters.

(b) (4)

7. Although the study results showed that the distributions of maternal age, ethnicity, and tobacco use were not balanced among the cohorts, the Wolters Kluwer study did not adjust the risk estimates for these confounding factors. However, based on the Slone/CDC study, the risk estimates did not change significantly when they adjusted one factor at a time for family history of birth defects, maternal age, race/ethnicity, pre-pregnancy BMI, smoking, alcohol, diabetes, folic acid intake, and epilepsy. Therefore, the impact of not adjusting for these risk factors on the risk estimates of Wolters Kluwer study is uncertain.
8. Lastly, cases in the Wolters Kluwer study were not validated. It is likely that the risk estimates are biased towards the null due to potential non-differential misclassification of study outcomes.

4.2 THE DENMARK STUDY

Although the Denmark study used nationwide data, only 108 women had exposure to TPM during the first trimester of pregnancy. It was not powered to examine the association between TPM exposure and risk of OCs. The adjusted prevalence odds ratios for TPM exposure and major birth defects provided by this study and the crude prevalence odds ratios for TPM exposure and OCs calculated by DEPI should be considered as exploratory analyses only. Another limitation is that cases from the primary care setting were not included in the study. Therefore, the prevalence rate of major birth defects may have been under-estimated in this study.

4.3 DIRECTION OF BIAS

The directions of bias associated with the study limitations in each study were summarized in Table 7.

Table 7. Study attributes and limitations and their potential impact on the association between TPM exposure during pregnancy and risk of OCs and MCMs

Direction of Bias	Slone/CDC Study	Wolters Kluwer Study	Denmark Study
Bias Towards No Association		<ul style="list-style-type: none"> • Over-estimation of exposure by assuming 100% compliance with prescriptions • Composite study outcome of oral clefts • Cases not validated • Small sample size • Misclassification of pregnancy based on delivery date 	<ul style="list-style-type: none"> • Over-estimation of exposure by assuming 100% compliance with prescriptions • Composite study outcome of oral clefts • Small sample size • Cases not validated
Bias Towards Positive Association	<ul style="list-style-type: none"> • Recall bias in reporting TPM exposure between cases and controls 		
Bias with Unknown Direction	<ul style="list-style-type: none"> • Confounding factors were not adjusted simultaneously • Reporting bias in reporting potential confounding factors, e.g., smoking, alcohol abuse 	<ul style="list-style-type: none"> • Confounding risk factors not adjusted • TPM monotherapy and polytherapy combined <div data-bbox="792 1039 1104 1228" style="background-color: #cccccc; width: 100%; height: 90px; margin-top: 10px;">(b) (4)</div>	<ul style="list-style-type: none"> • Maternal diabetes, obesity, folic acid intake, and alcohol use were not adjusted • TPM monotherapy and polytherapy combined • Cases limited to those who are diagnosed at hospitals and ambulatory care facilities

5 SUMMARY

In summary, each study has limitations, but with different directions of bias and significance. All three studies investigated the effect of TPM exposure during the first trimester of pregnancy on live birth infants. The fetal outcomes that ended in abortion (spontaneous or induced), or stillbirth could not be assessed. Overall, the Slone/CDC study provided higher risk estimates of OCs and MCMs associated with TPM exposure during the first trimester of pregnancy compared to the other two studies. The risks of OCs and MCMs were probably underestimated in the Wolters Kluwer study because most of the study limitations would bias the results towards no association between TPM

exposure during pregnancy and risk of OCs and MCMs. Those limitations along with the small sample size, might be responsible for the negative findings in the Wolters Kluwer study. The sponsor's comment that the Denmark study confirms an absence of a signal for an increased prevalence of MCMs with topiramate exposure is not supported because of the limited statistical power of the Denmark study.

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/s/

JING JU

01/20/2012

This review replaces the review dated December 28, 2011 by Jing Ju.

TAREK A HAMMAD

01/22/2012



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

Date: January 20, 2012

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II, OND, CDER

Through: Tarek A. Hammad, MD, PhD, MSc, MS, Deputy Director
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Diane K Wysowski, PhD, MPH, Team Leader
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: Review of sponsor's interim report entitled "Fetal outcomes retrospective topiramate exposure study (FORTRESS)."
Dated December 13, 2011

Drug Name(s): Qnexa (phentermine & topiramate)

Submission Number:

Application Type/Number: NDA 22580

Applicant/sponsor: Vivus

OSE RCM #: 2011-4184

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EXECUTIVE SUMMARY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), the interim report of the observational study (Fetal Outcomes Retrospective Topiramate Exposure Study (FORTRESS)) dated December 13, 2011, in support of the New Drug Application (NDA) of Qnexa was reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

The FORTRESS study is a retrospective cohort study of the association between topiramate (TPM) and congenital malformations using four data sources (HealthCore, OptumInsight, Kaiser Northern California, and Thomson Reuters). Although the Kaiser Southern California data was proposed in the study protocol, Vivus, the sponsor of Qnexa, clarified that the data from Kaiser Southern California were not available to be included in the study. The interim report provided study results from phase I analyses which addressed the primary study objectives and two secondary objectives based on automated data only.

The preliminary study results provided in this interim report showed that first trimester TPM exposure was associated with about a two-fold (center & propensity score decile-standardized prevalence ratio = 2.45, 95% confidence interval: 0.97-6.18, not statistically significant) increased risk of OCs compared with remote TPM exposure which was at least 120 days prior to the index pregnancy.

The interim report also showed that first trimester TPM exposure was associated with about a six-fold (center & propensity score decile-standardized prevalence ratio = 6.46, 95% confidence interval: 2.07-20.17) increased risk of OCs compared with women with similar medical profiles (SMP) but without TPM exposure in their first trimester of pregnancy. However, the unusually low prevalence of 0.29 OC cases per 1,000 births in the SMP cohort in the HealthCore database suggested that the sampling methods for the SMP cohort might have been problematic or the initial sample was an outlier that occurred by chance. Therefore, the pooled prevalence ratio of OCs for the TPM-exposed cohort vs. the SMP cohort could have been over-estimated. As a result, on January 13, 2012 in response to the sponsor's request to resample the SMP cohort, the FDA requested the sponsor to include all eligible study subjects in the SMP cohort for all study sites to

re-estimate the prevalence ratios. Therefore, the study results in the interim report for comparison of the TPM vs. SMP cohorts are likely to be changed.

(b) (4)

[REDACTED]. However, on January 12, 2012, the sponsor informed the FDA that the preliminary analyses for the MCMs were currently undergoing internal quality checks and the results will not be ready to be presented at the AC meeting.

One important study limitation is the limited sample sizes for the subgroup analyses (e.g., TPM high/low dose, short/long duration, monotherapy/polytherapy). Also, the sample size was further reduced in the propensity score stratification analyses. Therefore, depending on what is a clinically acceptable risk, the sample size in the TPM monotherapy subcohort is likely to be inadequate. Another study limitation associated with the use of claims data to identify exposure and outcomes was non-differential misclassification of exposure and outcome. The effect of non-differential misclassification of exposure and outcome usually biases the results toward the null (no association between TPM exposure and outcome). Lastly, this study only investigated the effect of TPM exposure during the first trimester of pregnancy on live birth infants and the fetal outcomes that ended in abortion (spontaneous or induced), or stillbirth could not be assessed.

In conclusion, the risks of OCs and MCMs associated with TPM use in the first trimester of pregnancy have not been fully answered in this interim report of the FORTRESS study due to the limited sample size in the TPM monotherapy subcohort, the pending study results using the entire SMP cohort, and the poor data quality issues with the analyses for MCMs.

1 BACKGROUND/HISTORY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), the interim report of the observational study (Fetal Outcomes Retrospective Topiramate Exposure Study (FORTRESS)) dated December 13, 2011, in support of the New Drug Application (NDA) for Qnexa was reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

Qnexa is a combination of two marketed products, phentermine and topiramate (TPM), for which the applicant is seeking approval for the treatment of obesity and overweight. If approved, Qnexa will be available in three fixed-dose combinations of phentermine/topiramate: 3.75mg/23mg, 7.5mg/46mg, and 15mg/92mg. Recent reports based on the registry data and an observational study from the U.S. and the U.K. have suggested that infants exposed to TPM in utero have an increased risk of oral clefts (OCs) and/or major congenital malformations (MCMs)^{1,2,3}.

A Complete Response letter to Vivus, the sponsor of Qnexa, was issued by FDA on October 28, 2010. An End of Review Conference was held on January 19, 2011, and a follow-up industry meeting was held on April 14, 2011, during which an observational study on the risk of congenital malformations, especially OCs, associated with maternal exposure to TPM during pregnancy was requested by the FDA. A draft study protocol (fetal outcomes retrospective topiramate exposure study (FORTRESS) dated May 25, 2011, was reviewed by DEPI and recommendations were sent to the sponsor. The final study protocol (dated September 6, 2011) and a draft summary pooled analysis plan (dated August 5, 2011) were reviewed by DEPI and recommendations were sent to the sponsor.

The interim report of the FORTRESS study results dated December 13, 2011, was based on the FORTRESS study protocol dated September 6, 2011. The preliminary study results will be discussed in the upcoming Advisory Committee meeting on Qnexa approval on February 22, 2012. On December 19, 2011, FDA requested more study results on the comparison between the TPM monotherapy subcohort and the similar medical profile (SMP) control cohort and study results with data from all data sources included in the analyses. On January 11, 2012, the sponsor responded to FDA's information request and informed FDA that data from the Kaiser Southern California research database were not available to be included in the analyses.

This review will provide an evaluation of the study methods and preliminary results based on data provided in the interim report of the FORTRESS study dated December 13, 2011.

2 REVIEW MATERIALS

Materials that were included in this review are:

- The interim report of the FORTRESS study dated December 13, 2011;
- FORTERESS data development plan (phase 1 final version 4.5) dated November 30, 2011;
- Vivus responses to FDA information request dated January 11, 2012, serial No. 0067.

3 RESULTS OF REVIEW

3.1 STUDY SYNOPSIS

The primary objectives of the FORTRESS study were to estimate the prevalence ratios of oral clefts (OCs) and major congenital malformations (MCMs) in newborns of women exposed to TPM during the first trimester of pregnancy when compared to (a) newborns of women with remote (at least 120 days prior to the index pregnancy) prior exposure to TPM or other antiepileptic drugs (AEDs); and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure. This study was a retrospective cohort study with four data sources (HealthCore, OptumInsight, Kaiser Northern California, and Thomson Reuters). As a result, a total of 1945 mother-baby dyads were included in the TPM-exposed cohorts from these data sources.

The OC prevalence ratios standardized by center were 2.36 (95% CI, 0.99-5.59) for TPM-exposed cohort vs. the formerly exposed (FE) comparison cohort and 5.44 (95% CI, 2.03-14.61) for the TPM cohort vs. the similar medical profile (SMP) comparison cohort. When standardized by propensity score decile and center, the prevalence ratios were 2.45 (0.97-6.18) for TPM vs. FE and 6.46 (2.07-20.17) for TPM vs. SMP. The prevalence ratios standardized by propensity score decile and center were 2.00 (0.71-5.68) for the TPM monotherapy subcohort vs. the FE cohort and 5.71 (1.75-18.58) for the TPM monotherapy subcohort vs the SMP cohort.

(b) (4)

Due to the possibility that the sampling methods of the initial SMP cohort in the HealthCore site may have been problematic or the initial SMP cohort was an outlier occurred by chance, on January 13, 2012, FDA requested the entire SMP cohort for all study sites to be used in the analyses and the results might be provided to FDA later. On January 12, 2012, the sponsor informed the FDA that the preliminary analyses on MCMs was currently undergoing internal quality check and the results in the interim report will not be presented at the AC meeting.

3.2 STUDY OBJECTIVES

3.2.1 Study Objectives:

The primary objectives were:

- 1) to estimate the prevalence ratio of OCs in newborns of women exposed to TPM during the first trimester of pregnancy when compared to: (a) newborns of women with remote (at least 120 days prior to the index pregnancy) prior exposure to TPM or other AEDs (referred to as the FE cohort throughout this review); and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure (referred to as the SMP cohort throughout this review);
- 2) to estimate the prevalence ratio of MCMs in newborns of women exposed to TPM during the first trimester of pregnancy when compared to: (a) newborns of women in the FE cohort; and (b) newborns of women in the SMP cohort.

The secondary objectives were:

- 1) to estimate the prevalence of OCs and other MCMs in newborns of women exposed to specific doses of TPM during the first trimester and to evaluate any dose response;

- 2) to monitor for any signals of specific MCMs, aside from OCs, associated with TPM exposure in the first trimester;

3.2.2 Reviewer Comments:

The study objectives are appropriate.

3.3 STUDY DESIGN

3.3.1 Study Design:

This study is a retrospective cohort study.

3.3.2 Reviewer Comments:

This reviewer agrees that a retrospective cohort study is appropriate.

3.4 DATA SOURCES

3.4.1 Data Sources:

The final study protocol dated September 6, 2011, proposed to use data from the HealthCore Integrated Research Database (HIRD), OptumInsight Normative Health Information (NHI) database, Kaiser Permanente Northern and Southern California (KPNC & KPSC) Research Databases, and the Thomson Reuters MarketScan Multi-State Medicaid Research Databases.

The HealthCore HIRD database contains longitudinal health claims data on approximately 45 million individuals with medical and pharmacy benefits back to 2001. Medical records can be requested for about 75% of subjects in this database.

The OptumInsight NHI database contains medical and pharmacy claims data from 1994 with a cumulative enrollment of approximately 14 million patients. Medical records can be requested for subjects in a portion of the research database.

The KPNC and KPSC research databases contain automated clinical and pharmacy data that capture live born delivery, diagnoses of malformation, and dispensing of prescription medications. More than 3.3 million members are served by the KPNC and a similarly sized population is served by KPSC.

The Thomson Reuters MarketScan Multi-State Medicaid Research Database contains healthcare service use of individuals covered by Medicaid programs in several

geographically dispersed states. The Multi-State Medicaid database dates back to 1999 and contains an average of 10 million Medicaid enrollees each year.

3.4.2 Reviewer Comments:

The proposed use of the HealthCore HIRD database, OptumInsight NHI database, KPNC and KPSC Research Databases, and the Thomson Reuters MarketScan Multi-State Medicaid Research Databases is acceptable. However, this interim report did not list the Kaiser Northern California as one of the data sources. As the FDA requested the sponsor to include the Kaiser Northern California data into all analyses, the sponsor responded that “The Kaiser Permanente data included in the interim report dated December 13, 2011 came exclusively from Kaiser Permanente of Northern California. The interim report inadvertently misidentified this data as having come from Kaiser Permanente of Southern California. No data from Kaiser Permanente of Southern California was used in the Fortress study.”

3.5 STUDY POPULATION

3.5.1 Proposed Study Population:

The study population included women with a record of live birth during the study period and an identifiable newborn with at least 90-day post-delivery enrollment. Women eligible to enroll in this study included those who: 1) had at least 6 months of continuous enrollment in the health plan prior to the presumed conception date, and 2) were between the ages of 15 and 49 years on the delivery date.

Women were excluded if they had: 1) a history of infection with one of the TORCH agents (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis, varicella-zoster, and parvovirus B19), 2) a history of alcohol abuse or substance abuse, or 3) an exposure to thalidomide or isotretinoin during the 6 months preceding the presumed conception date or at any point during the pregnancy.

3.5.2 Reviewer Comments:

The reviewer agrees that the study population and the inclusion/exclusion criteria are appropriate.

3.6 EXPOSURES

3.6.1 Exposures:

A Mother-baby pair exposed to TPM during the first trimester of pregnancy was defined as those for whom prescription data indicate exposure to TPM at any dose during the first trimester. Exposure to TPM or other AEDs was ascertained using National Drug Codes (NDCs) from prescription claims data. A woman was considered exposed if TPM was dispensed during the exposure window (defined in the next paragraph in this Section) or if an earlier dispensing included enough supply to carry over into the exposure period. Exposure to TPM was defined in two ways: 1) as an indicator variable for whether there was first trimester exposure; and 2) as a numerical variable based on calculated average daily dose.

The exposure window of the first trimester was defined as: 1) for women who delivered at term, the earliest possible date of conception through 91 days following the latest possible date of conception, or from 287 through 168 days before delivery for singleton births or from 273 through 147 days before delivery for multiple births (note: multiple births are usually delivered earlier than single births); 2) for women with a diagnosis code of premature delivery and the length of gestation is not specified, the earliest possible date of conception through 91 days following the latest possible date of conception, or from 252 through 133 days before delivery; and 3) for those with some delivery codes indicating length of gestation, as the first 91 days of the specified gestation period.

For the FE comparison cohort of mother-infant pairs with remote prior exposure to TPM or any other AEDs before the index pregnancy, eligible cohort members were those exposed to TPM or other AEDs from the earliest continuous enrollment up to 120 days before the estimated earliest conception period for the index pregnancy. This cohort excluded mothers who were exposed to TPM or other AEDs during the pregnancy or within 120 days before the estimated conception date.

The SMP comparison cohort consisted of mothers with similar medical profiles as the TPM cohort (seizure/epilepsy, migraine, or other), but without current exposure to TPM during pregnancy or during the 120 days prior to the earliest conception date. The SMP cohort did not contain any mothers without a history of seizure/epilepsy, migraine,

or other TPM indication. The SMP cohort was frequency matched to the TPM-exposed cohort at a 7:1 ratio by indication. Members of the SMP cohort may also be included in the FE cohort.

3.6.2 Reviewer Comments:

This reviewer agrees that the definitions of exposure and exposure window are appropriate.

3.7 DISEASE OUTCOMES OF INTEREST

3.7.1 Proposed Study Outcomes:

Primary Outcomes:

One of the primary outcomes was nonsyndromic OCs that are not associated with diagnosed or suspected chromosomal or genetic defects. OCs were identified using ICD-9-CM diagnosis codes or CPT procedure codes associated with claims for physician services or hospitalization that occur within 30 days of the presumed delivery date on the mother's claims or within 365 days of birth date on the infant's claims. Mother-infant pairs who had additional claims data suggesting syndromic malformations or genetic or chromosomal defects did not qualify as cases.

The other primary outcomes were MCMs which were defined as conditions present at birth resulting from malformation, deformation, or disruption in one or more parts of the body and having serious adverse effects on the health, development, or functional ability. MCMs were identified using ICD-9-CM diagnosis codes within 30 days of the delivery date on the mother's claims or within 365 days of birth date on the infant's claim. Mother-infant pairs who have additional claims data suggesting syndromic malformations or genetic or chromosomal defects did not qualify as cases.

Secondary Outcomes:

Specific MCMs other than OCs (not pre-specified) were explored as secondary endpoints.

3.7.2 Reviewer Comments:

The primary outcomes of OCs and MCMs in this interim report were based on the claims data only and no validation effort was undertaken. Therefore, the study results should be considered as preliminary only.

3.8 STUDY COVARIATES

3.8.1 Study Covariates

Potential confounders that were evaluated in the stratified analyses included maternal age, indications for TPM use, maternal diabetes, exposure to known or suspected teratogens, geographic area, race/ethnicity, infant sex, delivery type (single/multiple birth), and premature birth. Each potential confounder was evaluated one at a time by comparing results standardized by center with results that were standardized by center and one potential confounder. A change of less than 10% in the prevalence ratio was used as an indicator that confounding for that variable was of negligible importance.

These study covariates listed above and other potential confounders (maternal conditions of seizures/epilepsy, migraine, schizophrenia, episodic mood disorders, anxiety disorders, chronic pain, obesity, and hypertension; medications of valproate, carbamazepine, phenytoin, Phenobarbital, other AEDs, folic acid antagonists, other teratogens; maternal smoking, and calendar year based on the earliest date of conception) were also controlled simultaneously by center-specific propensity score decile.

3.8.2 Reviewer Comments:

These study covariates and the evaluations of confounding are appropriate based on previous studies in the literature^{3,4}. It would be more complete if the study could have also evaluated the study covariates of maternal alcohol use, maternal and family history of MCMs, and mother's parity. However, this reviewer agrees that it is not feasible to evaluate these variables in this study.

3.9 SAMPLE SIZE

3.9.1 Sample Size

A total of 1,945 mother-baby dyads who had exposure to TPM during their first trimester of pregnancy were included in the TPM-exposed cohort. A total of 13,512

mother-infant pairs were included in the FE comparison cohort and 13,614 mother-infant pairs were included in the SMP comparison cohort.

3.9.2 Reviewer Comments:

The sample size in the TPM-exposed cohort was reduced from the estimated 2,300 to 1,945 in the interim analyses. The sample size in the SMP comparison cohort was reduced from the estimated 16,100 to 13,614 (TPM: SMP ratio of 1:7). The sample size in the FE control cohort was increased from the estimated 10,000 to 13,512 (TPM: FE ratio of 1:7). Based on the previous power calculations performed by the FDA's Office of Biostatistics (Table 1), the smallest possible relative risk (RR) that could be ruled out with 80% power should be within the range of 3.40-4.47 for OCs and within the range of 1.31-1.40 for MCMs given the study size in the interim analyses. However, the sample sizes for the subgroup analyses (e.g., TPM high/low dose, short/long duration, monotherapy/polytherapy) were more limited. Also, the sample size was further reduced in the propensity score stratification analyses. Therefore, depending on what is a clinically acceptable risk, the sample size in the TPM monotherapy subcohort is likely to be inadequate.

Table 1: Estimates of the smallest possible RR that could be ruled out under the study size and power restrictions and the associated number of excess events above the background rate (data source: Statistical review, Office of Biostatistics, FDA)

TPM-Exposed Dyads	Control Cohort	Power	Oral Clefts		MCMs	
			Rule Out RR of	Excess Events*	Rule Out RR of	Excess Events*
1,400	9,800 (ratio of 1:7)	80%	4.47	4.2	1.40	10.0
2,200	15,400 (ratio of 1:7)	80%	3.40	2.9	1.31	7.9

* Excess events in number of events per 1,000 patients above the background rate of 1.2 events per 1,000 (for OCs) or 25 events per 1,000 (for MCMs)

3.10 ANALYSES

3.10.1 Proposed Analyses

Descriptive statistics were computed for demographic variables and relevant covariates and summarized within each database. Prevalence estimates of OCs and other MCMs were computed in each database.

In the main analyses & pooled analysis for prevalence ratios of OCs and MCMs, stratified analyses were conducted within each data source. The stratified tables were forwarded to (b) (4) for the final pooled analysis, which also involved stratification by study center. Summary prevalence ratio estimates standardized to the TPM-exposed cohort were reported.

A second approach involved stratification by propensity score deciles calculated within each data source. The variables that were included to generate propensity scores include maternal age, infant sex, calendar year, geographic region, smoking, use of valproate, carbamazepine, phenytoin, other AEDs, folic acid antagonists, known or suspected teratogens, history of epilepsy, migraine, affective disorder, diabetes, hypertension, and obesity. Strata of propensity score were defined by deciles of the propensity score distribution.

Two secondary analyses were conducted to assess: 1) the dose-response relationship by estimating the effect of 100 mg or less per day versus more than 100 mg per day of TPM during the first trimester; 2) the duration-response relationship by evaluating whether the TPM effect varies according to the number of exposed days within the first trimester.

An exploratory study was conducted to assess the presence of signals for increased risks of MCMs by organ system affected. The main outcome was the prevalence ratio of organ system-specific MCMs among women with first trimester exposure to TPM when compared to the control groups.

3.10.2 Reviewer Comment:

Because of the low count of OC cases in each study site and the large number of potential confounding factors that need to be controlled, the propensity score approach is

the preferred method versus the covariate-based stratified analysis. The strata in the propensity score approach should be classified by quartiles instead of deciles of propensity score distribution to minimize the zero or low count problem associated with stratification by deciles. The distributions of study covariates within each stratum (propensity score quartiles) should be provided to the FDA to examine whether these covariates were balanced across study cohorts. Also, infant sex should not be included in the logistic regression model to generate propensity scores as this is not a factor affecting the probability of each mother using TPM during early pregnancy.

Due to the limited sample size and rare outcomes, some of the subgroup analyses may not be able to provide stable estimates and the results could be difficult to interpret.

3.11 STUDY RESULTS

3.11.1 Study Results

The number of OC cases in each study center was very small. A summary of the number of OC cases and characteristics of each cohort, stratified by center were presented in Table 1.

Table 2. Sample size, number of OC cases, and patient characteristics by study cohort and by center

Characteristics	Topiramate (TPM) Cohort (n=1,945)	Formerly Exposed (FE) Cohort (n=13,512)	Similar Medical Profile (SMP) Cohort (n=13,614)
Number of infants			
HealthCore	495	2,935	3,465
Kaiser	119	2,044	833
OptumInsight	748	4,196	5,235
Thomson Reuters	583	4,337	4,081
Number of OC cases (prevalence per 1,000 births)			
HealthCore	3 (6.06)	3 (1.02)	1 (0.29)
Kaiser	0 (0.00)	4 (1.96)	0 (0.00)
OptumInsight	3 (4.01)	8 (1.91)	4 (0.76)
Thomson Reuters	1 (1.72)	6 (1.38)	4 (0.98)
Percentage with maternal characteristic			
Caucasian race			

Characteristics	Topiramate (TPM) Cohort (n=1,945)	Formerly Exposed (FE) Cohort (n=13,512)	Similar Medical Profile (SMP) Cohort (n=13,614)
HealthCore	NA	NA	NA
Kaiser	59	53	48
OptumInsight	83	82	79
Thomson Reuters	80	65	69
Epilepsy indication			
HealthCore	11	7	12
Kaiser	17	9	17
OptumInsight	11	7	11
Thomson Reuters	18	13	19
Migraine indication			
HealthCore	66	36	73
Kaiser	66	34	67
OptumInsight	66	43	69
Thomson Reuters	43	21	46
Premature birth			
HealthCore	11	11	9
Kaiser	13	12	9
OptumInsight	11	11	9
Thomson Reuters	9	11	10
Diabetes			
HealthCore	6	5	4
Kaiser	8	5	4
OptumInsight	5	6	5
Thomson Reuters	7	5	4
Hypertension			
HealthCore	6	4	4
Kaiser	7	4	4
OptumInsight	7	5	4
Thomson Reuters	9	5	6
Obesity			
HealthCore	2	1	1
Kaiser	39	29	24
OptumInsight	11	9	8
Thomson Reuters	12	10	13
Exposure to possible teratogen during first trimester			
HealthCore	21	16	12

Characteristics	Topiramate (TPM) Cohort (n=1,945)	Formerly Exposed (FE) Cohort (n=13,512)	Similar Medical Profile (SMP) Cohort (n=13,614)
Kaiser	15	7	11
OptumInsight	19	15	14
Thomson Reuters	32	18	21
AED poly-exposures			
HealthCore	8	0 ^a	<1
Kaiser	11	0 ^a	2
OptumInsight	7	0 ^a	1
Thomson Reuters	16	0 ^a	1

^a By definition, no antiepileptic drug (AED) therapy during pregnancy.

As shown in Table 3, the OC prevalence ratio for the TPM-exposed cohort vs. FE comparison cohort standardized by center was 2.36 (95% CI, 0.99-5.59). The center-standardized OC prevalence ratio for TPM cohort vs. the similar medical profile (SMP) comparison cohort was 5.44 (95% CI, 2.03-14.61). When standardized by propensity score and center, the prevalence ratios were 2.45 (0.97-6.18) for TPM vs. FE and 6.46 (2.07-20.17) for TPM vs. SMP.

The sponsor claimed in the interim report that (b) (4)

[REDACTED]

[REDACTED] Upon FDA request, the prevalence ratios for the TPM monotherapy subcohort vs. the SMP cohort were provided which were presented in Table 4.

Table 3. Standardized prevalence ratios of OCs for TPM-exposed cohort compared with the FE and the SMP control cohorts

Standardization Variables	PR of TPM vs. FE	95% CI	PR of TPM vs. SMP	95% CI
Crude	2.32	0.99-5.44	5.44	2.03-14.60
Study center	2.36	0.99-5.59	5.44	2.03-14.61
Age & center	2.52	1.06-6.00	5.86	2.17-15.81
Region & center	2.57	1.08-6.11	5.25	1.93-14.27
Diabetes & center	2.38	1.00-5.66	5.09	1.87-13.82
Teratogenic drug exposure & center	2.37	0.99-5.65	6.05	2.25-16.23
TPM indication & center	2.10	0.86-5.12	6.30	2.34-16.96
Race/ethnicity & center	2.37	1.00-5.64	5.52	2.00-15.26
Infant sex & center	2.33	0.98-5.53	5.47	2.04-14.67
Delivery type & center	2.30	0.97-5.47	5.35	1.99-14.35
Premature birth & center	2.34	0.99-5.55	5.50	2.05-14.74
Propensity score & center	2.45	0.97-6.18	6.46	2.07-20.17

Table 4. Prevalence ratios of OCs standardized by propensity score decile and center for TPM monotherapy compared with the FE and SMP cohorts by TPM dose and duration

Exposure Category	PR of TPM vs. FE	95% CI	PR of TPM vs. SMP	95% CI
Overall	2.00	0.71-5.68	5.71	1.75-18.58
TPM low dose*	2.12	0.60-7.56	5.75	1.44-22.93
TPM high dose**	1.85	0.41-8.26	5.65	1.14-27.91
TPM short duration of therapy***	1.67	0.37-7.49	4.65	0.94-23.04
TPM long duration of therapy****	2.31	0.65-8.23	6.74	1.68-27.08

* low-dose: daily TPM doses of 100 mg or less

** high-dose: daily TPM doses greater than 100 mg

***short-duration: equal or less than 38 days, 38 days, 51 days, or 43 days of TPM use during the first trimester in data sites of HealthCore, OptumInsight, Kaiser, Thomson Reuters, respectively

****long-duration: more than 38 days, 38 days, 51 days, or 43 days of TPM use during the first trimester in data sites of HealthCore, OptumInsight, Kaiser, Thomson Reuters, respectively

(b) (4)

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3.11.2 Reviewer Comment:

As the propensity score stratification is the preferred method over the covariate-based stratified analysis, this review will focus on the prevalence ratios standardized by propensity score decile and center. For the TPM-exposed cohort vs. FE control cohort, the propensity score and center-standardized prevalence ratio was 2.45 (0.97-6.18), which suggests that first trimester TPM exposure was associated with about a two-fold increased risk of OCs compared with remote TPM exposure which was at least 120 days prior to the index pregnancy. For the TPM-exposed cohort vs. the SMP control cohort, the propensity score and center-standardized prevalence ratio was 6.46 (2.07-20.17), which suggests that first trimester TPM exposure was associated with about a six-fold increased risk of OCs compared to no TPM exposure in the first trimester of pregnancy.

The investigation from the HealthCore study site into the sampling of their SMP cohort suggested that the initial selected SMP cohort might be a statistical aberration, capturing only 1 case of OC, whereas upon repeated samples the mean was 5 cases of OCs. DEPI agrees that this initial sampling of SMP cohort in the HealthCore data could be an outlier occurred by chance or the sampling method for the SMP cohort could be problematic and the prevalence ratios for the TPM vs. SMP cohorts could have been over-estimated.

The sponsor raised a question about resampling the SMP cohort at all study sites. Recognizing that the original sampling of the SMP cohort in the HealthCore site could be an outlier by chance, resampling the SMP cohort in the HealthCore site alone might be acceptable under certain conditions. However, the analyses would be considered post-hoc using the re-sampled SMP cohort and the study results could be manipulated by picking a favorable SMP sample. To minimize the potential bias, DEPI suggests that the sponsor use all eligible study subjects from the SMP control cohort at all study sites to re-assess the prevalence ratios of OCs and MCMs.

This reviewer disagrees with the sponsor's claim that the FE cohort offers a more valid comparison than the SMP cohort. The prevalence ratios using different comparison

cohorts, FE & SMP, provide different information and should be interpreted accordingly. The comparison with the FE cohort would inform whether the timing of exposure matters in the development of OCs. The risk estimates using the SMP comparison cohort would inform whether first-trimester TPM exposure was associated with an increased risk of OCs controlling for underlying conditions (TPM indications). Therefore, it is important to provide the risk estimates using the SMP comparison cohort in the FORTRESS Study.

One important limitation of the interim analyses is the misclassification bias. As the study investigators pointed out that the use of claims data to identify exposure and outcomes has certainly introduced some, presumably non-differential misclassification bias. The effect of non-differential misclassification of exposure and outcome usually biases the results toward the null (no association between TPM exposure and outcome).

4 SUMMARY

The study results from this interim report were based on claims-only analyses without validation effort and would be considered preliminary. The preliminary study results showed that first trimester TPM exposure was associated with about a two-fold (not statistically significant) increased risk of OCs compared with remote TPM exposure which was at least 120 days prior to the index pregnancy.

Data from the interim report also showed that first trimester TPM exposure was associated with about a six-fold increased risk of OCs compared to no TPM exposure in their first trimester of pregnancy. However, the unusually low prevalence of 0.29 OC cases per 1,000 births in the SMP cohort at the HealthCore site suggested that the sampling methods for the SMP cohort may have been problematic or the initial sample was a chance outlier. Therefore, the pooled prevalence ratio of OCs for the TPM-exposed cohort vs. the SMP cohort could have been over-estimated. FDA has requested the sponsor to use all eligible study subjects in the SMP cohort for all study sites to re-estimate the prevalence ratios and the results are likely to be changed.

(b) (4)

This reviewer disagrees with the sponsor's claim that the FE cohort offers a more valid comparison than the SMP cohort. The prevalence ratios using different comparison cohorts, FE & SMP, provide different information and should be interpreted accordingly. The comparison with the FE cohort would inform whether the timing of exposure matters in terms of OC risk. The risk estimates using the SMP comparison cohort is as important as these estimates would inform whether the first-trimester TPM exposure is associated with an increased risk of OCs controlling for underlying conditions (TPM indications). Therefore, the FORTRESS study should use all eligible study subjects in the SMP cohorts at all study sites to re-assess the prevalence ratios of OCs and MCMs and provide the study results to the FDA for evaluation.

One important study limitation is the limited sample sizes for the subgroup analyses (e.g., TPM high/low dose, short/long duration, monotherapy/polytherapy). Also, the sample size would be further reduced in the propensity score stratification analyses. Therefore, depending on what is a clinically acceptable risk, the sample size in the TPM monotherapy subcohort is likely to be inadequate. Another study limitation associated with the use of claims data to identify exposure and outcomes was non-differential misclassification of exposure and outcome. The effect of non-differential misclassification of exposure and outcome usually biases the results toward the null (no association between TPM exposure and outcome). Lastly, this study only investigated the effect of TPM exposure during the first trimester of pregnancy on live birth infants and the fetal outcomes that ended in abortion (spontaneous or induced), or stillbirth could not be assessed.

In conclusion, the risks of OCs and MCMs associated with TPM use in the first trimester of pregnancy have not been fully answered in this interim report of the FORTRESS study due to the limited sample size in the TPM monotherapy subcohort, the pending study results using the entire SMP cohort, and the poor data quality issues with the analyses for MCMs.

5 RECOMMENDATIONS TO BE SENT TO THE SPONSOR

- *Please obtain more mother-baby dyads for the FORTRESS study (e.g. from the Kaiser Southern California research database as proposed in the study protocol) to ensure an adequate sample size in the TPM monotherapy subcohort.*
- *Please re-assess the prevalence ratios of OCs and MCMs using all eligible study subjects in the SMP cohorts at all study sites and submit study results to the FDA.*
- *Please provide data on the distributions of study covariates within each stratum with the propensity score stratification approach to the FDA to examine whether these covariates were balanced across study cohorts.*
- *Please incorporate FDA's recommendations (including the following three sub-bullets) regarding the study protocol (dated September 6, 2011) and the draft summary pooled analysis plan (dated August 5, 2011) into the study.*
 - *You should validate all potential MCM cases that will be identified in the study cohorts. Alternatively, the sponsor may restrict the validation to all of the 10 most common specific MCMs. The validation should be done in the study cohorts to enhance the validity of the study results and only validated cases should be included in the final analyses. The PPV should be estimated using both the base case definition and the secondary, more restrictive case definition. A sampling approach is not preferred because of the challenges of specifying appropriate sampling fraction and acceptable precision margins for PPV given the heterogeneity of malformations. Additionally, low PPV values present a challenge in utilizing the validation data in estimating the risk.*
 - *The propensity score stratification analysis is preferred over the stratified analysis by individual covariate and the strata should be classified by quartiles instead of deciles of propensity score distribution. A sensitivity analysis using propensity score matching should be performed.*

- *Infant sex should not be included in the logistic regression model to generate propensity scores as this is not a factor affecting the probability of a mother using TPM during early pregnancy*

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-
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TAREK A HAMMAD
01/22/2012

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

Date: January 12, 2012

Reviewer: Vicky Borders-Hemphill, Pharm.D.
Drug Use Data Analyst
Division of Epidemiology II
Office of Surveillance and Epidemiology

Team Leader: Hina Mehta, Pharm.D.
Drug Utilization Data Analysis Team Leader,
Division of Epidemiology II
Office of Surveillance and Epidemiology

Deputy Director: Laura Governale, Pharm.D., MBA
Deputy Director for Drug Utilization
Division of Epidemiology II
Office of Surveillance and Epidemiology

Division Director: Judy Staffa, Ph.D., RPh
Division of Epidemiology II (DEPI II)
Office of Surveillance and Epidemiology

Subject: Phentermine and Topiramate use in women of child-bearing potential

Drug Name(s): Phentermine (Adipex-P and generic) and Topiramate (Topamax[®] and generic)

Application Type/Number: ANDA 85-128, ANDA 88-023 and various; NDA 20-505, and NDA 20-844

Applicant/sponsor: Teva and Ortho McNeil Janssen

OSE RCM #: 2011-4184

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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EXECUTIVE SUMMARY

The Division of Metabolism and Endocrinology Products (DMEP) is reviewing NDA 22-580, Qnexa (phentermine/topiramate), resubmitted on October 17, 2011, with a Risk Evaluation and Mitigation Strategy (REMS) to minimize the risk of congenital malformation by preventing fetal exposure to the product. The sponsor's new proposed indication is for obese patients with a body mass index (BMI) over 30 or overweight patients with a BMI over 27 who do not have child-bearing potential (which excludes those females aged ≥ 18 -54 years from the indication), and who have at least one co-morbidity, such as high blood pressure, type 2 diabetes, or abdominal obesity. The sponsor, Vivus, plans to implement labeling for Qnexa with a designation of Pregnancy Category X. As part of the review process, a second Advisory Committee (AC) meeting is planned for February 22, 2012. In preparation for this AC on February 22, 2012, the Division of Epidemiology II (DEPI II) analyzed the use of phentermine and topiramate.

Data findings are as follows:

- Topiramate prescriptions increased by 97% from 4.6 million to 9.1 million prescriptions dispensed from the 12-month period ending in October 2003 to the 12-month period ending in October 2011.
 - 76% to 79% of total dispensed topiramate prescriptions were dispensed to females
 - the majority of topiramate prescriptions dispensed to females were dispensed to females aged 18-54 years
- Phentermine prescriptions increased by 124% from 3.1 million to 6.9 million prescriptions dispensed from the 12-month period ending in October 2003 to the 12-month period ending in October 2011.
 - 85% to 86% of total dispensed phentermine prescriptions were dispensed to females
 - the majority of phentermine prescriptions dispensed to females were dispensed to females aged 18-54 years
- Overall, there was low concurrent use between the two products. Approximately, 2% to 3% of all patients as well as female patients had a concurrent prescription claim for topiramate and phentermine. Around 1% to 2% of males had concurrent prescription claims.
- The sponsor's proposed targeted treatment population includes all aged males and any females aged 55 years or older which account for around one-third of those presently exposed to topiramate.
- According to office-base physicians, the most common diagnosis code associated with the use of topiramate was ICD-9 346.9 MIGRAINE NOS
 - Diagnoses associated with the use of topiramate specifically for the treatment of obesity included ICD-9 307.5 EATING DISORDERS NEC/NOS and ICD-9 278.0 OBESITY represented around 1% of drug use mentions.

1 INTRODUCTION

The Division of Metabolism and Endocrinology Products (DMEP) is reviewing NDA 22-580, Qnexa (phentermine/topiramate), resubmitted on October 17, 2011, with a new indicated population and a Risk Evaluation and Mitigation Strategy (REMS) to minimize the risk of congenital malformation by preventing fetal exposure to the product. As part of the review process, a second Advisory Committee (AC) meeting is planned for February 22, 2012. In preparation for this AC on February 22, 2012, this review examines the extent of use for topiramate and phentermine products as monotherapy and concurrent therapy in the general population as well as in females of child bearing potential.

National prescription utilization for phentermine and topiramate products was examined by patient age [0-17 years (sub level 0-11, 12-17), 18-54 years (sub level 18-40, 41-54), 55+ years] and sex, and by prescriber specialty for nine 12-month periods ending in October 2011. An analysis of indications for topiramate use between two cumulative time periods (January 1996 through December 2004 compared with January 2005 through October 2011) was also conducted. Additionally, this review examines the concurrent use of phentermine and topiramate overall and among patients aged [0-17 years (sub level 0-11, 12-17), 18-54 years (sub level 18-40, 41-54), 55+ years] and by sex during four 12-month periods ending in October 2011.

1.1 BACKGROUND

On July 15, 2010, the Endocrine and Metabolic Advisory Committee Advisory Committee (AC) meeting was held to discuss safety and efficacy for Qnexa (phentermine/topiramate), NDA 22-580, for the treatment of obesity, including weight loss and maintenance of weight loss. Concerns were raised regarding the risk of congenital malformation and teratogenicity, and the panel voted 10-6 against approval of the new drug application.

Vivus resubmitted the NDA on October 17, 2011, with a Risk Evaluation and Mitigation Strategy (REMS) to minimize the risk of fetal exposure and a new proposed indication for obese patients with a body mass index (BMI) over 30 or overweight patients with a BMI over 27 who do not have child-bearing potential (which excludes those females aged ≥ 18 -54 years from the indication), and who have at least one co-morbidity, such as high blood pressure, type 2 diabetes, or abdominal obesity. Vivus plans to implement labeling for Qnexa with a designation of Pregnancy Category X. A second Advisory Committee is planned for February 22, 2012 to discuss this NDA resubmission.

1.2 PRODUCTS INCLUDED

Phentermine is an anorexigenic agent used as an adjunct to exercise, behavioral modification, and caloric restriction in the short-term management of exogenous obesity.¹

Topiramate (Topamax®) is an antiepileptic agent indicated for initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized

¹ Adipex-P® (phentermine) [package insert]. Manufactured for Gate Pharmaceuticals, Sellersville, PA 18960 By Teva Pharmaceuticals USA, Sellersville, PA 18960. July 2005.

tonic-clonic seizures, and in patients ≥ 2 years of age with seizures associated with Lennox-Gastaut syndrome, and treatment for adults for prophylaxis of migraine headache.²

Drug name	Dosage Form and Strength	Original Approval date
Phentermine products: [(Phentermine HCl: Adipex-P, Suprenza, phentermine generics); Phentermine resin complex generics]	Tablets and Capsules: 37.5mg Tablets and Capsules; orally disintegrating: 15mg and 30mg Extended release capsules: EQ 15mg base and EQ 30mg base	May 1959
Topiramate products: (Topamax [®] and generic formulations; Topamax [®] sprinkle):	Tablets: 25 mg, 50 mg, 100 mg, 200 mg Capsules: 15 mg, 25 mg	December 1996 (Antiepileptic) August 2004 (Migraine prophylaxis)

2 METHODS AND MATERIALS

2.1 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales Perspectives[™] was used to determine the various retail and non-retail channels of distribution for phentermine and topiramate products. Sales data for 12-month period ending in September 2011 indicated that approximately 83% of topiramate products were distributed to outpatient retail pharmacies; 6% were to mail order pharmacies, and 11% to non-retail settings. For phentermine products, approximately 90% of bottles and packages were distributed to outpatient retail pharmacies; less than 1% were to mail order pharmacies, and 9% to non-retail settings.³ Neither mail order nor non-retail settings were included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (see Appendix 2 for detailed database descriptions).

2.2.1 National Outpatient Prescription Utilization Analysis

The IMS Health, Vector One[®]: National (VONA) was used to estimate the number of prescriptions dispensed from the outpatient retail pharmacy setting for phentermine and topiramate products overall and stratified by age [0-17 years (sub level 0-11, 12-17), 18-54 years (sub level 18-40, 41-54), 55+ years], gender, and prescriber specialty for nine 12-month periods ending in October 2003 to October 2011.

² Topamax[®] (topiramate) [package insert]. Manufactured for Janssen Pharmaceuticals, Inc, Titusville, NJ 08560 By Janssen Ortho, LLC, Gurabo, Puerto Rico 00778. July 2011.

³ IMS Health, IMS National Sales Perspectives[™], MATs September 2006-MAT September 2011, Extracted 11-10-11. File: NSPC 2011-4184 phentermine topiramte channels.xls

2.2.2 Associated Diagnoses Analysis

Indications for use were obtained from the SDI's Physician's Drug and Diagnosis Audit (PDDA), a survey of office-based physicians, by ICD-9 4-digit diagnosis codes for topiramate products during two cumulative time periods of January 1996 through December 2004 and January 2005 through October 2011.

2.2.3 Nationally Projected Number of Outpatient Topiramate and Phentermine Prescription Claims by Age and Gender Analysis and Concurrent Drug Analysis

The Wolters Kluwer Source Lx[®] Concurrency Product Analyzer (WKCPA) tool was used to determine the number of U.S. outpatient prescription claims for phentermine and topiramate products, as well as to examine episodes of concurrent use among patients with an overlapping prescription claim for topiramate or phentermine products. The patient population was selected based on the occurrence of one topiramate or phentermine claim for a duration of at least one day with a 90 day study look back period starting in November 2007 and ending in the 12-month period October 2008, October 2009, October 2010, and October 2011. An episode of concurrency is identified when a patient has overlapping therapy days with a topiramate or phentermine product. A grace period of 50% was applied to the end of days supply on a prescription claim for each product to compensate for under compliance and to determine continuation of therapy.

3 RESULTS

3.1.1 National Outpatient Prescription Utilization Analysis for Topiramate and Phentermine

3.1.1.1 Topiramate prescriptions: age, female gender, and strength

Figure 1 in Appendix 1 shows the number of topiramate prescriptions dispensed through U.S. outpatient retail pharmacies in total and to female patients stratified by age from the 12-month period ending in October 2003 through the 12-month period ending in October 2011. Total topiramate prescriptions dispensed increased by 97% from 4.6 million prescriptions dispensed in the 12-month period ending in October 2003 to 9.1 million prescriptions dispensed in the 12-month period ending in October 2011.

Approximately 76% to 81% of total dispensed topiramate prescriptions were dispensed to females during each 12-month period examined. During the latest 12-month period ending in October 2011 approximately 7.4 million prescriptions (81% of total) of topiramate were dispensed to females.

Of the topiramate prescriptions dispensed to female patients the majority were dispensed to females of child-bearing age 18-54 years with 2.7 million (76% of all prescriptions to females) prescriptions dispensed during 12-month period ending in October 2003 and 5.3 million prescriptions (72% of all prescriptions to females) dispensed during 12-month period ending in October 2011. Nearly equal proportions of topiramate prescriptions dispensed to females in the 18-40 year sub age group (48% to 49%; 1.3 million to 2.6 million prescriptions) were dispensed to those in the 41-54 year sub age group (51% to 52%; 1.4 million to 2.7 million prescriptions). Approximately 571,000 (16% of all prescriptions to females) topiramate prescriptions were dispensed to females aged 55 years or older during the 12-month period ending in October 2003 and 1.7 million prescriptions (23% of all prescriptions to females) were dispensed during the 12-month period ending in October 2011. Topiramate prescriptions dispensed to pediatric female patients aged 0-17 years ranged from 275,000 prescriptions (8% of all prescriptions to females) dispensed during the 12-month period ending in October 2003 to 354,000 prescriptions (5% of all prescriptions to females) during the 12-month period ending in October 2011. Of the topiramate prescriptions dispensed to female patients

of the 0-17 age group, a greater proportion were dispensed to those aged 12-17 years (65% to 74%; 180,000 to 262,000 prescriptions) compared to those aged 0-11 years.

There was a gradual increase in dispensed topiramate prescriptions during the time period examined. Trends were similar among each 12-month period.

Figure 2 in Appendix 1 shows the number of topiramate prescriptions stratified by strength dispensed to female patients from U.S. outpatient retail pharmacies. During the most recent 12-month period ending October 2011, nearly equal proportions of topiramate prescriptions dispensed to females were dispensed for the 100 mg (32% or 2.3 million prescriptions), 25 mg (31% or 2.3 million prescriptions), and 50 mg (28% or 2.1 million prescriptions) strengths.

3.1.1.2 Phentermine prescriptions: age, female gender, and strength

Figure 3 in Appendix 1 shows the number of phentermine prescriptions dispensed through U.S. outpatient retail pharmacies in total and to female patients stratified by age from the 12-month period ending in October 2003 through the 12-month period ending in October 2011. Total phentermine prescriptions dispensed increased by 124% from 3.1 million prescriptions dispensed in the 12-month period ending in October 2003 to 6.9 million prescriptions dispensed in the 12-month period ending in October 2011.

Approximately 85% to 86% of total dispensed phentermine prescriptions were dispensed to females during each 12-month period examined. During the latest 12-month period ending in October 2011 approximately 5.9 million prescriptions (85% of total) of phentermine were dispensed to females.

Of the phentermine prescriptions dispensed to female patients the majority were dispensed to females aged 18-54 years with 2.2 million prescriptions (84% of all prescriptions to females) dispensed during the 12-month period ending in October 2003 and 5 million prescriptions (84% of all prescriptions to females) dispensed during the 12-month period ending in October 2011. Of the phentermine prescriptions dispensed to females aged 18-54 years, there were a slightly greater proportion of prescriptions dispensed to females in the 18-40 year sub age group (55% to 58%; 1.2 million to 2.8 million prescriptions) than to those in the 41-54 year sub age group (42% to 45%; 1 million to 2.2 million prescriptions). Approximately 385,000 phentermine prescriptions (15% of all prescriptions to females) were dispensed to females aged 55 years or older during the 12-month period ending in October 2003 and 919,000 prescriptions (16% of all prescriptions to females) were dispensed during the 12-month period ending in October 2011. There were 16,000 phentermine prescriptions dispensed (less than 1% of all prescriptions to females) to pediatric females aged 0-17 years during the 12-month period ending in October 2003 and 25,000 prescriptions dispensed (less than 1% of all prescriptions to females) during the 12-month period ending in October 2011.

There was a gradual increase in dispensed phentermine prescriptions during the time period examined. Trends were similar among each 12-month period.

Figure 4 in Appendix 1 shows the number of phentermine prescriptions stratified by strength dispensed to female patients from U.S. outpatient retail pharmacies. During the most recent 12-month period ending in October 2011, approximately 5.1 million prescriptions or 86% of prescriptions dispensed to females were for the 37.5 mg strength.

3.1.1.3 Rates of Topiramate and Phentermine Prescriptions dispensed to U.S. Women (prescriptions/100,000 women)

Table 1 in Appendix 1 shows the rates of prescriptions dispensed for topiramate and phentermine products to U.S. women (prescriptions/100,000 women) stratified by age from outpatient retail

pharmacies for years 2003 through 2010. Utilization data were adjusted for U.S. females of child-bearing potential by U.S. census age groups to account for the U.S. population growth in the population of interest.

In the 12-month period ending in October 2010, there were 6,446 topiramate prescriptions dispensed per 100,000 women among patients aged 18-54 years, an 84% increase in dispensed prescriptions per 100,000 women since year 2003. For the same period, there were 6,154 phentermine prescriptions dispensed per 100,000 women among patients aged 18-54 years, a 112% increase in dispensed prescriptions per 100,000 women since year 2003.

3.1.2 National Outpatient Prescription Utilization by Prescriber Specialty Analysis for Topiramate and Phentermine

3.1.2.1 Topiramate prescriptions: prescriber specialty

Figure 5 in Appendix I shows the number of prescriptions dispensed for topiramate stratified by top 10 prescribing specialties from U.S. outpatient retail pharmacies. During the time period examined, Neurologists were the top prescriber specialty of topiramate prescriptions dispensed from outpatient retail pharmacies. During the 12-month period ending in October 2011, Neurologists accounted for 30% of topiramate dispensed prescriptions followed by General Practitioners/Family Medicine/Doctor of Osteopathy, Psychiatrists, and Internal Medicine Physicians accounting for approximately 21%, 12%, and 11% of dispensed prescriptions, respectively. Several prescriber specialties showed large percentage increases in dispensed prescriptions from the first 12-month period examined ending in October 2003 to the last 12-month period examined ending in October 2011. Dispensed prescriptions from General Practitioners/Family Medicine/Doctor of Osteopathy increased by 343%, Internal Medicine increased by 255%, Nurse Practitioners increased by 343%, Physicians Assistants increased by 1008%, and Pediatricians increased by 123%. Dispensed prescriptions from Neurologists increased by 71%. During the same comparative time period dispensed prescriptions by Psychiatrists decreased by 9%.

3.1.2.2 Phentermine prescriptions: prescriber specialty

Figure 6 in Appendix I shows the number of prescriptions dispensed for phentermine stratified by top 10 prescribing specialties from U.S. outpatient retail pharmacies. During the time period examined, General Practitioners/Family Medicine/Doctor of Osteopathy were the top prescriber specialty of phentermine prescriptions dispensed from outpatient retail pharmacies followed by Internal Medicine. During the 12-month period ending in October 2011, General Practitioners/Family Medicine/Doctor of Osteopathy accounted for 39% of phentermine dispensed prescriptions followed by Internal Medicine, Nurse Practitioners, and Obstetrician/Gynecologists with 19%, 8%, and 7%, respectively of dispensed prescriptions. Most prescriber specialties showed percentage increases in dispensed prescriptions from the first 12-month period ending in October 2003 to the last 12-month period ending in October 2011. Prescriptions from General Practitioners/Family Medicine/Doctor of Osteopathy dispensed prescriptions increased by 85%, Internal Medicine increased by 101%, Nurse Practitioners increased by 672%, Obstetrician/Gynecologists increased by 107%, Physicians Assistants increased by 658%, and Pediatricians increased by 125% over the time period examined.

3.1.3 Analysis of Diagnoses Encountered in the Office-Based Practice Setting for Topiramate⁴

An analysis of diagnoses encountered in office-based physician practices in the U.S. was conducted for two cumulative time periods from January 1996 through December 2004 and from January 2005 through October 2011 (*data not shown*).

During the cumulative time period from January 1996 through December 2004, the most common diagnosis code associated with the use of topiramate was ICD-9 346.9 MIGRAINE NOS with 25% of drug use mentions. Diagnoses associated with obesity included ICD-9 307.5 EATING DISORDERS NEC/NOS at 0.6% of drug use mentions and ICD-9 278.0 OBESITY at 0.8% of drug use mentions for topiramate.

During the cumulative time period from January 2005 through October 2011, the most common diagnosis associated with the use of topiramate was ICD-9 346.9 MIGRAINE NOS at 46% of drug use mentions. Diagnoses associated with obesity included ICD-9 307.5 EATING DISORDERS NEC/NOS at 0.7% of drug use mentions and ICD-9 278.0 OBESITY at 0.3% drug use of mentions for topiramate.

3.1.4 Number of Topiramate and Phentermine Outpatient Prescription Claims by Patient Age and Sex Analysis and Concurrent Drug Analysis

Table 2 in Appendix 1 shows the total number of patients with a prescription claim for topiramate and phentermine alone or concurrently stratified by patient age from the 12-month period ending in October 2008 to the 12-month period ending in October 2011.

Table 3 and Figure 7 in Appendix 1 shows the total number of *female* patients with a prescription claim for topiramate and phentermine alone or concurrently stratified by age from the 12-month period ending in October 2008 to the 12-month period ending in October 2011.

3.1.4.1 Total Topiramate Patients: age and sex

The number of patients with a topiramate prescription claim increased by 19% from 1.9 million patients during the 12-month period ending in October 2008 to 2.3 million patients during the 12-month period ending in October 2011.

The majority of patients with a prescription claim for topiramate were aged 18-54 years throughout the time period examined. Of the 2.3 million patients with a prescription claim for topiramate, 1.6 million were aged 18-54 years during the 12-month period ending in October 2011.

The number of female patients with a prescription claim for topiramate increased from 1.5 million patients during 12-month period ending in October 2008 to 1.8 million patients during the 12-month period ending in October 2011.

The majority of female patients with a claim for topiramate were females of child-bearing potential aged 18-54 years with 1.1 million patients (75% of all females) during the 12-month period ending in October 2008 to 1.3 million patients (74% of all females) during the 12-month period ending in October 2011. There were nearly equal proportions of female patients with a claim for topiramate in the 18-54 sub groups with 705,000 female patients aged 18-40 years (53% of females aged 18-54

⁴ SDI: Physician Drug and Diagnosis Audit. Data extracted 12-5-11. File: PDDA_2011-4184_topi_phent_4ddx_1996-2011_12-5-11.xls

years) during the 12-month period ending in October 2011 and 631,000 female patients (47% of females aged 18-54 years) aged 41-54 years. Around 352,000 female patients (20% of females) with a topiramate claim were aged 55 years or older during the 12-month period ending in October 2011 while 104,000 female patients (6% of females) were pediatric aged 0-17 years.

3.1.4.2 Total Phentermine Patients: age and gender

The number of patients with a phentermine prescription claim increased by 31% from 2.5 million patients during the 12-month period ending in October 2008 to 3.3 million patients in the 12-month period ending in October 2011.

The majority of patients with a prescription claim for phentermine were aged 18-54 years throughout the time period examined. Of the 3.3 million patients with a prescription claim for phentermine 2.7 million patients were aged 18-54 years during the 12-month period ending in October 2011.

The number of female patients with a prescription claim for phentermine increased from 2.1 million patients during the 12-month period ending in October 2008 to 2.7 million patients during the 12-month period ending in October 2011.

The majority of female patients with a claim for phentermine were females of child-bearing potential aged 18-54 years with 1.8 million patients (84% of all females) during the 12-month period ending in October 2008 to 2.3 million patients (85% of all females) during the 12-month period ending in October 2011. There was a greater proportion of female patients with a claim for phentermine in the 18-54 year sub group of 18-40 years with 1.4 million female patients (58% of females aged 18-54 years) during the 12-month period ending in October 2011 compared to the sub group of 41-54 years with 965,000 female patients (42% of females aged 18-54 years). Around 397,000 female patients (15% of all females) with a phentermine claim were aged 55 years or older while less than 1% of female patients with a phentermine claim were pediatrics aged 0-17 years.

3.1.4.3 Patients with Concurrent Claims for Topiramate and Phentermine (Figure 7)

There was low concurrent use between phentermine and topiramate products. Approximately 2% to 3% of all patients as well as female patients that had a concurrent prescription claim for topiramate and phentermine products. Around 1% to 2% of males had concurrent prescription claims (*data not shown*).

Patients with concurrent claims for both phentermine and topiramate increased from 42,000 during the 12-month period ending in October 2008 to around 66,000 patients during the 12-month period ending in October 2011; a 57% increase in patients with concurrent claims.

The number of female patients with concurrent claims steadily increased from 38,000 female patients during the 12-month period ending in October 2008 to around 57,000 female patients during the 12-month period ending in October 2011.

Of the 57,000 female patients with concurrent prescription claims 49,000 patients (85% of all females) were aged 18-54 years during the 12-month period ending in October 2011.

Approximately 8,000 female patients (14% of all females) with concurrent prescriptions claims were aged 55 years and greater while 300 female patients were pediatrics (less than 1% of total) aged 0-17 years during the 12-month period ending in October 2011.

4 DISCUSSION

Vivus proposed to exclude females aged 18-54 years from the Qnexa treatment patient population. Dispensed prescription data showed that females aged 18-54 years accounted for the majority of the present users of topiramate. The rates of prescriptions dispensed for topiramate or phentermine to U.S. women aged 18-54 years (prescriptions/100,000 women) increased substantially from year 2003 to year 2010. Data from the concurrency analysis suggested that the concurrent use of these drugs in females aged 18-54 years increased by almost 50% during the time period examined. Although the analysis of diagnoses encountered in office-based physician practices did not evaluate these associated diagnoses by gender and the concurrency analysis did not assess indications for use associated with episodes of concurrency, the analysis of diagnoses encountered in office-based physician practices suggested that topiramate for weight control represented a relatively small proportion (around 1%) of its overall use. Mentions associated with diagnoses of “Eating Disorders NEC/NOS” (ICD-9 307.5) and “Obesity” (ICD-9 278.0) for the pediatric population aged 0-17 years as well as for those adults aged 55 years or older appeared to be uncommon.⁵ Trends in prescribing patterns of topiramate for weight loss did not differ during the two time periods examined. Whereas, the proportion of mentions by office based physicians for migraine increased from 25% to 46% of mentions from before approval of topiramate for the migraine indication (prior to year 2004) to after.

Vivus’ proposed targeted treatment population includes all aged males and any females aged 55 years or older. This proposed target population accounted for around one-third of those presently exposed to topiramate according to prescription and patient claims data.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that these products are distributed primarily to the outpatient retail setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

The dispensed prescription and patient count estimates are based on national retail pharmacy estimates, but no statistical tests were performed to determine statistical significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

Diagnoses associated with drug use were obtained using SDI’s PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, small sample size and the relatively low usage of these products for uncommon diagnoses limits the ability to identify trends in the data and to stratify such data further by age, thus a cumulative time period of data was provided and demographics were not provided.

SDI uses the term “drug uses” to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. Ordinarily, a “drug use” does not necessarily result in prescription being generated; however, to obtain national estimates of use of topiramate products for the diagnosis of

⁵ SDI: Physician Drug and Diagnosis Audit. Data extracted 12-5-11. File: PDDA_2011-4184_topi_phent_4ddx_age_gender_2005-2011_12-5-11.xls

obesity-related conditions, several assumptions were made. First, we assumed that all drug use mentions from the PDDA office-based physician survey panel resulted in the issuance of a prescription. Second, we assumed that these prescriptions were then taken to the pharmacy and a product was dispensed.

In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. SDI recommends caution when interpreting nationally projected estimates of annual uses or mentions that fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

WKCPA analysis provides rates of concurrency amongst patients with at least one outpatient prescription claim for topiramate and phentermine that have overlapping days of supply from November 2007 through to October 2011. This does not include data from mail order pharmacies. This analysis provides an estimate of exposure of the two drugs around the same time but does not reveal the intention of the prescriber(s) for use as a combination weight loss product. Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Therefore, summing patients across years is not advisable and will result in overestimates of patient counts. Data

5 CONCLUSIONS

Both phentermine and topiramate prescriptions steadily increased over the time period analyzed. The data suggest that each product was dispensed primarily to females and those aged 18 to 54 years. Topiramate use for weight control represents a relatively small proportion of its use. According to office-base physicians, diagnoses associated with the use of topiramate specifically for the treatment of obesity included ICD-9 307.5 EATING DISORDERS NEC/NOS and ICD-9 278.0 OBESITY represented around 1% of drug use mentions.

There was low concurrent use between phentermine and topiramate. Approximately 2% to 3% of all patients as well as those that were female had a prescription claim for phentermine concurrently with topiramate. Male patients appeared to show a slightly lower level of concurrency than females (1%-2%).

6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

Figure 1

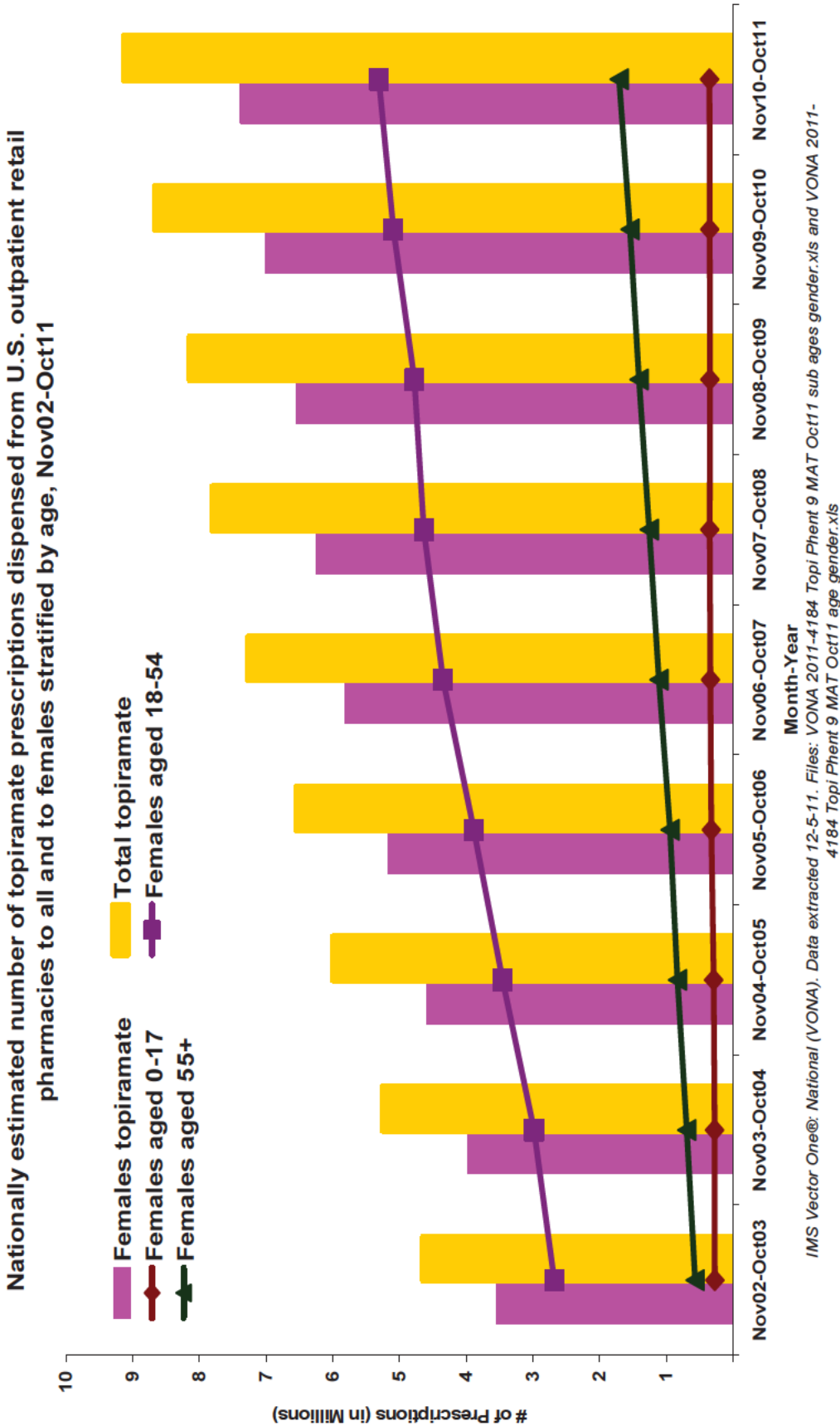


Figure 2

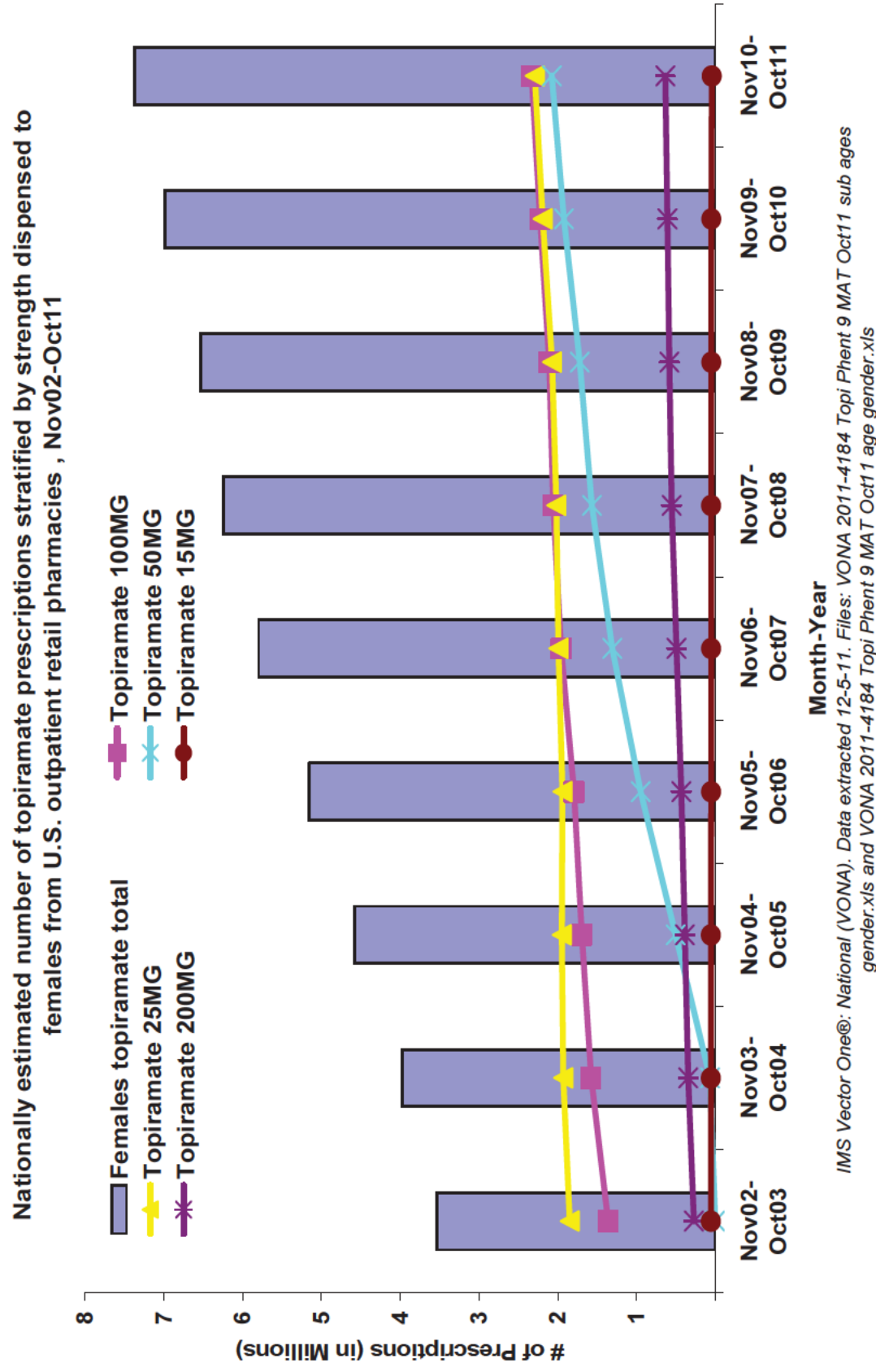


Figure 3

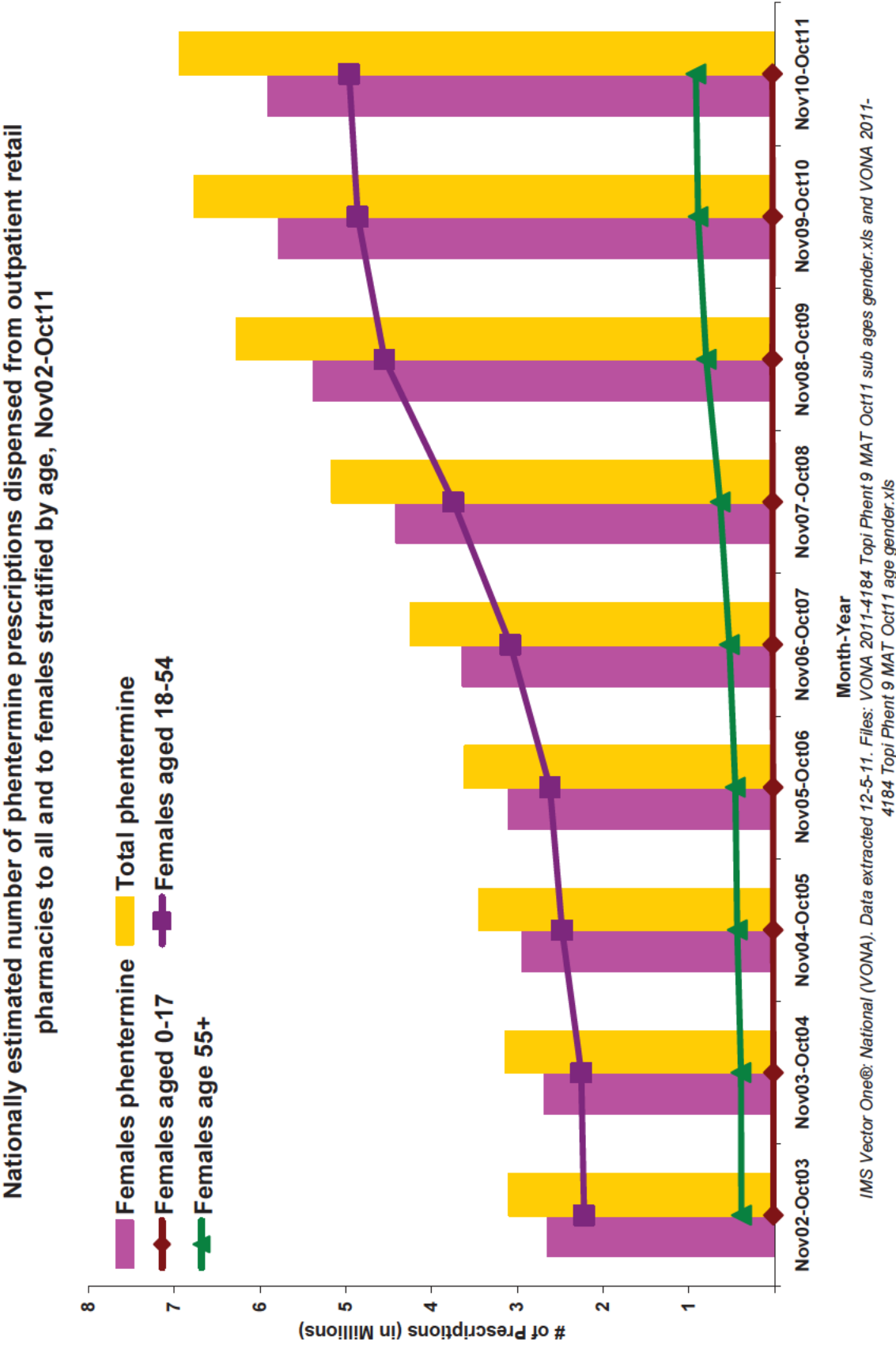


Figure 4

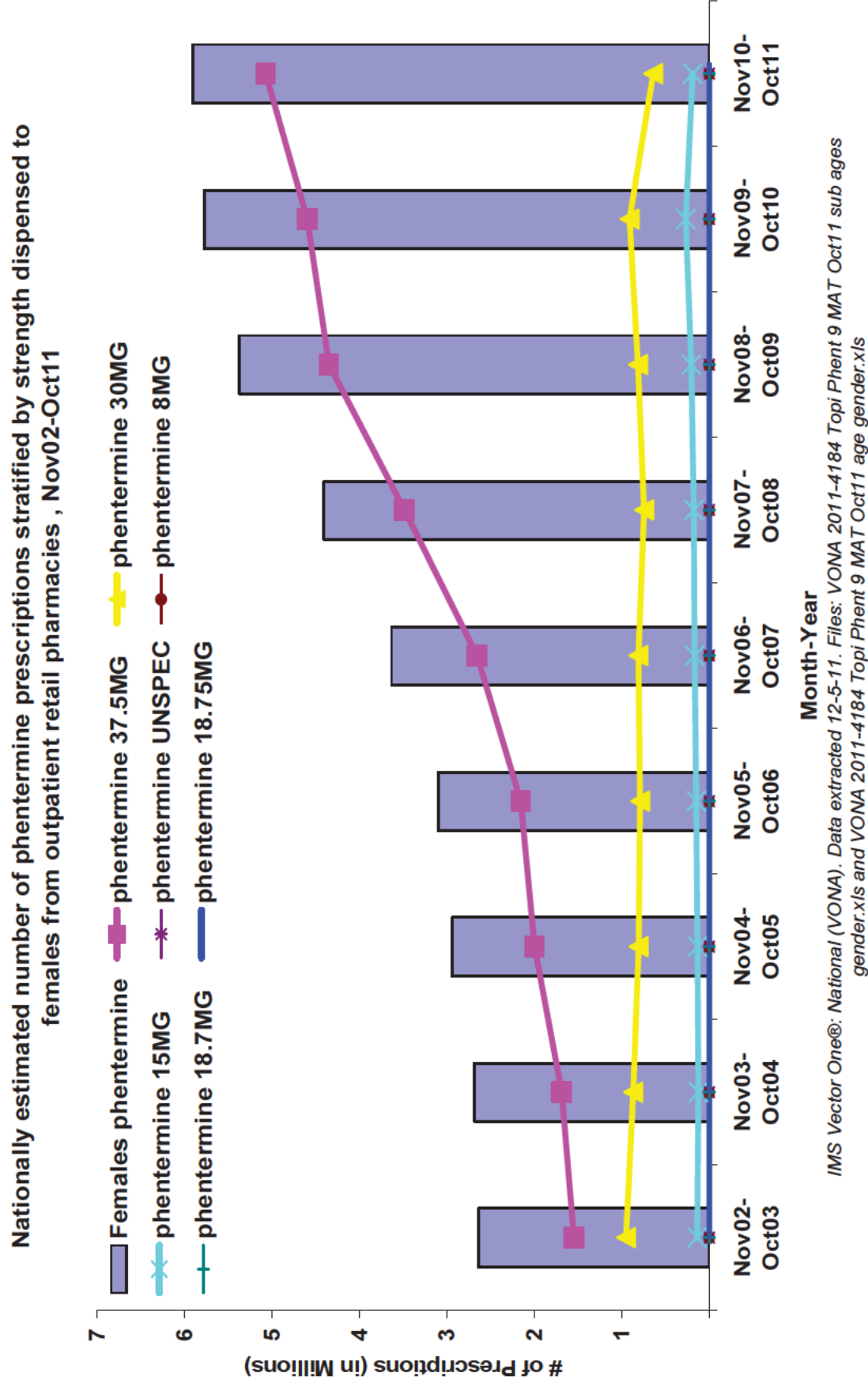


Table 1

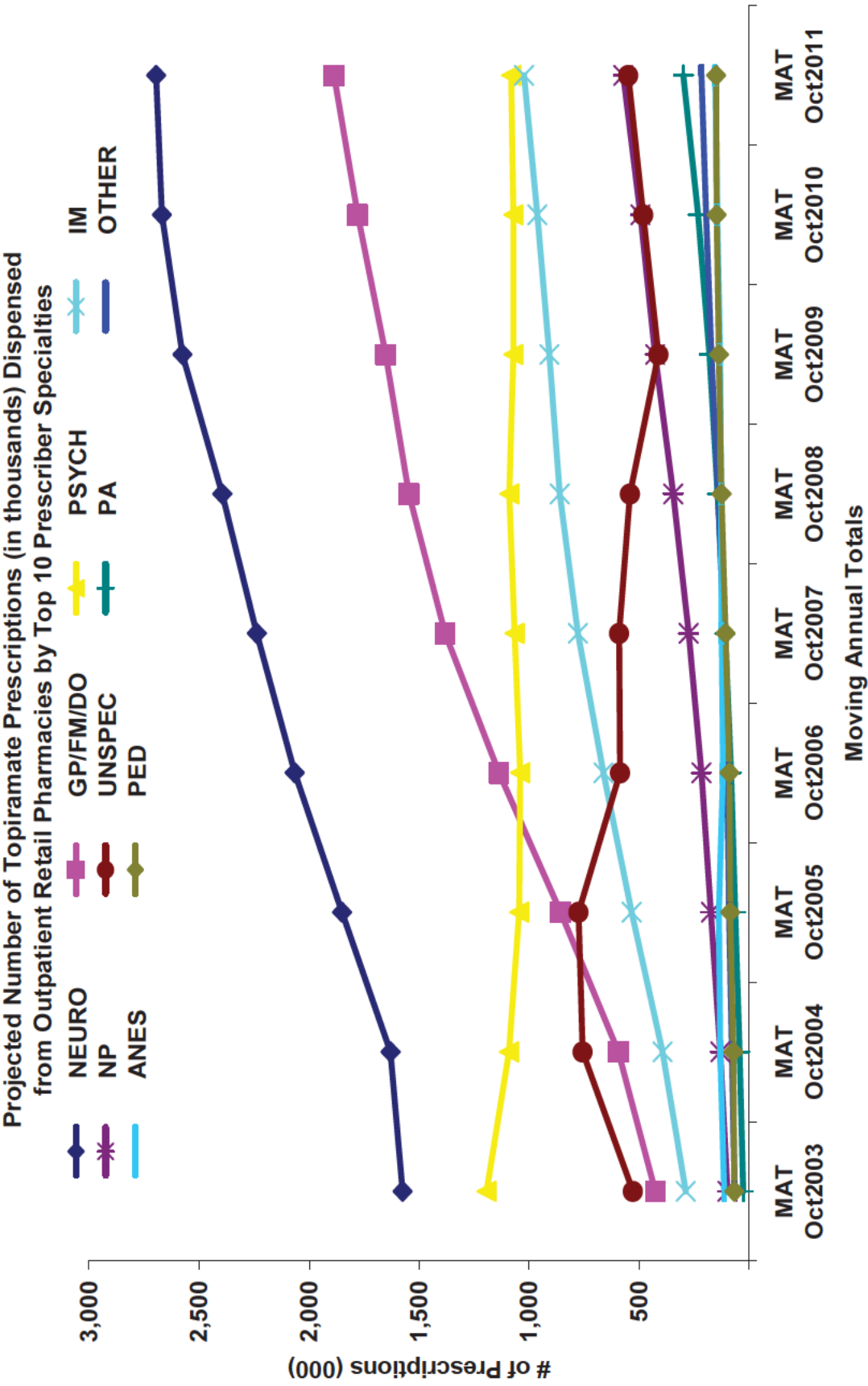
Number of topiramate or phentermine prescriptions dispensed to females per 100,000 women (U.S. Census) stratified by age, 12-month periods ending October 2003-October 2010

		Nov02 - Oct03	Nov03 - Oct04	Nov04 - Oct05	Nov05 - Oct06	Nov06 - Oct07	Nov07 - Oct08	Nov08 - Oct09	Nov09 - Oct10		
		Female Rx per Female U.S.	Female Rx per Female U.S.	Female Rx per Female U.S.	Female Rx per Female U.S.	Female Rx per Female U.S.	Female Rx per Female U.S.	Female Rx per Female U.S.	Female Rx per Female U.S.		
		pop	pop	pop	pop	pop	pop	pop	pop	pop	% change
Total Market		4,180	4,467	5,010	5,449	6,165	6,902	7,653	8,106		93.9%
topiramate		2,392	2,666	3,052	3,405	3,790	4,047	4,201	4,438		85.5%
0-17		770	777	807	904	937	969	955	958		24.4%
18-54		3,504	3,883	4,477	5,013	5,582	5,927	6,094	6,446		84.0%
55+		1,612	1,921	2,250	2,496	2,866	3,165	3,459	3,705		129.8%
phentermine		1,787	1,801	1,958	2,045	2,374	2,855	3,453	3,668		105.3%
0-17		44	44	47	52	61	67	68	66		50.9%
18-54		2,903	2,936	3,210	3,380	3,957	4,793	5,804	6,154		112.0%
55+		1,090	1,088	1,181	1,211	1,363	1,594	1,953	2,139		96.3%

IMS Vector One®: National (VONA). Data extracted 12-5-11. Files: VONA 2011-4184 Topi Phent 9 MAT Oct11 sub ages gender2.xls and and US Census Data Annual Estimates of the Resident Population by Sex and Selected Age Groups for the United States: April 1, 2002 to July 1, 2009. U.S. Census Bureau, Population Division, U.S. Dept of Commerce, December 2011.

Projections of the Population by Selected Age Groups and Sex for the United States: 2010 to 2050 U.S. Census Bureau, Population Division, U.S. Dept of Commerce, December 2011.

Figure 5



IMS Vector One®: National (VONA). Data extracted 12-5-11. Files: VONA_2011-4184_Topi_Phent_9_MAT_Oct11_prescriber.xls

Figure 6

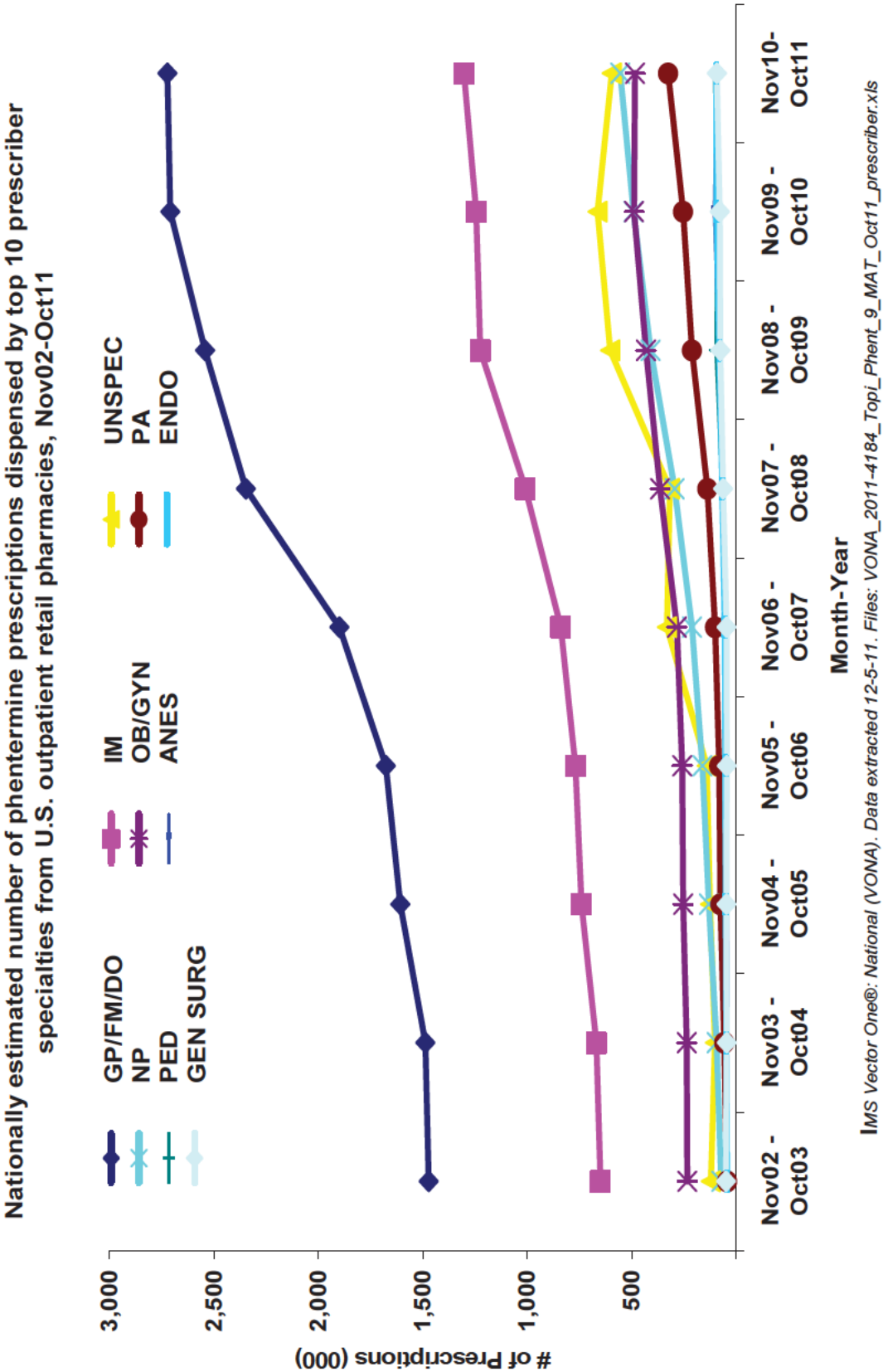


Table 2

Total patients with concurrent topiramate and phentermine prescription claims stratified by age, Nov07-Oct11

	November 2007-October 2008				November 2008-October 2009				November 2009-October 2010				November 2010-October 2011			
	Total Patient Count	Concurrent Patients	% Concurrent	Total Patient Count	Concurrent Patients	% Concurrent	Total Patient Count	Concurrent Patients	% Concurrent	Total Patient Count	Concurrent Patients	% Concurrent	Total Patient Count	Concurrent Patients	% Concurrent	Total Patient Count
Total PHENTERMINE	2,505,612	42,141	1.7%	2,914,818	43,701	1.5%	3,189,992	57,443	1.8%	3,278,393	65,964	2.0%				
Patient age 0-17	13,343	280	2.1%	15,712	251	1.6%	17,808	284	1.6%	19,127	444	2.3%				
Patient age 0-11	1,745	13	0.7%	2,781	14	0.5%	3,805	67	1.8%	4,042	51	1.3%				
Patient age 12-17	11,598	267	2.3%	12,932	237	1.8%	14,003	217	1.5%	15,085	393	2.6%				
Patient age 18-54	2,054,903	35,406	1.7%	2,411,738	36,529	1.5%	2,632,286	47,420	1.8%	2,705,322	54,268	2.0%				
Patient age 18-40	1,139,461	18,423	1.6%	1,383,888	20,038	1.4%	1,519,394	25,798	1.7%	1,554,467	29,515	1.9%				
Patient age 41-54	915,442	16,984	1.9%	1,027,850	16,491	1.6%	1,112,892	21,623	1.9%	1,150,855	24,753	2.2%				
Patient age 55+	406,805	6,114	1.5%	438,135	6,130	1.4%	481,122	8,976	1.9%	496,759	10,290	2.1%				
Patient age other	30,561	341	1.1%	49,233	792	1.6%	58,776	763	1.3%	57,187	963	1.7%				
Total TOPIRAMATE	1,900,398	42,141	2.2%	2,004,124	43,701	2.2%	2,169,149	57,443	2.6%	2,263,152	65,964	2.9%				
Patient age 0-17	139,802	280	0.2%	154,207	251	0.2%	168,080	284	0.2%	168,076	444	0.3%				
Patient age 0-11	41,261	13	0.0%	45,873	14	0.0%	48,466	67	0.1%	47,254	51	0.1%				
Patient age 12-17	98,542	267	0.3%	108,334	237	0.2%	119,614	217	0.2%	120,822	393	0.3%				
Patient age 18-54	1,348,119	35,406	2.6%	1,417,074	36,529	2.6%	1,527,748	47,420	3.1%	1,590,312	54,268	3.4%				
Patient age 18-40	680,084	18,423	2.7%	736,502	20,038	2.7%	804,368	25,798	3.2%	835,372	29,515	3.5%				
Patient age 41-54	668,035	16,984	2.5%	680,572	16,491	2.4%	723,380	21,623	3.0%	754,940	24,753	3.3%				
Patient age 55+	382,584	6,114	1.6%	392,098	6,130	1.6%	428,917	8,976	2.1%	456,660	10,290	2.3%				
Patient age other	29,894	341	1.1%	40,746	792	1.9%	44,404	763	1.7%	48,105	963	2.0%				

±Claims from U.S. commercial, Medicare Part D, Cash and Medicaid plans. *Age is at first claim during calendar year

Source Wolters Kluwer Health's Source® Lx. CPA tool 4 MAT ending October 2011. Extracted December 2011. File WKCPA 2011-4184 WORKING FILE 12-14-11.xls

Table 3

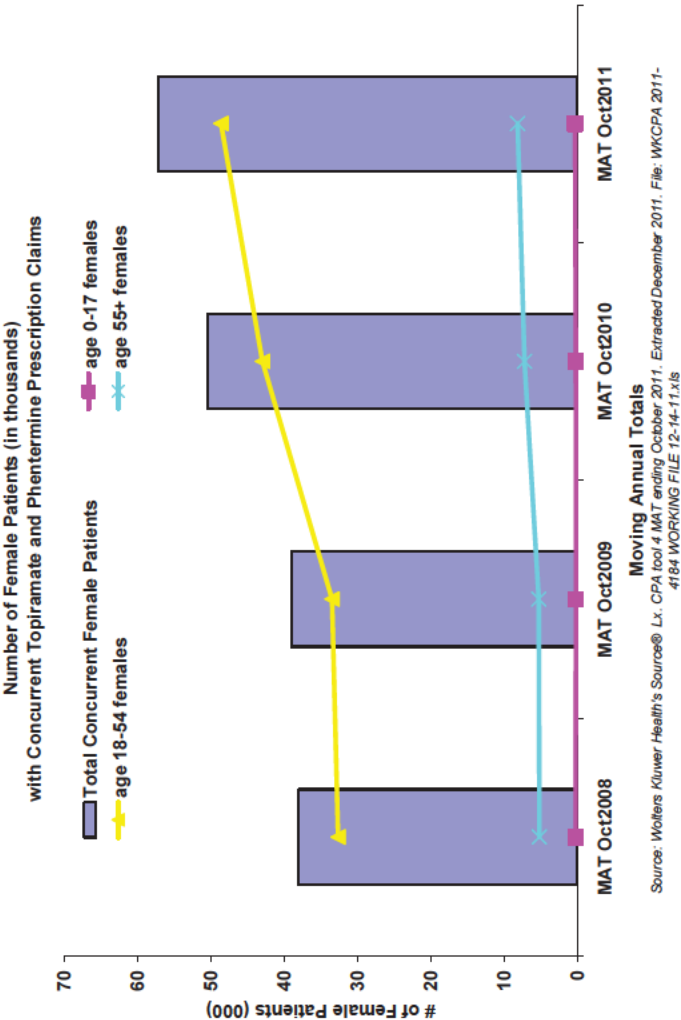
Total female patients with concurrent topiramate and phentermine prescription claims stratified by age, Nov07-Oct11

	November 2007-October 2008					November 2008-October 2009					November 2009-October 2010					November 2010-October 2011				
	Total		Female		% Concurrent	Total		Female		% Concurrent	Total		Female		% Concurrent	Total		Female		% Concurrent
	Patient Count	Female Patient	Patient Count	Female Patient		Patient Count	Female Patient	Patient Count	Female Patient		Patient Count	Female Patient	Patient Count	Female Patient		Patient Count	Female Patient	Patient Count	Female Patient	
Total PHENTERMINE	2,123,998	38,034	1,8%	2,461,182	1.8%	2,675,852	50,441	2,740,795	57,168	1.9%	2,740,795	57,168	2,740,795	57,168	1.9%	2,740,795	57,168	2,740,795	57,168	2.1%
Patient age 0-17	10,493	222	2.1%	12,239	1.4%	13,978	212	15,027	315	1.5%	15,027	315	15,027	315	1.5%	15,027	315	15,027	315	2.1%
Patient age 12-17	1,222	13	1.1%	2,010	0.2%	2,625	37	2,944	13	1.4%	2,944	13	2,944	13	1.4%	2,944	13	2,944	13	0.4%
Patient age 18-54	9,271	209	2.3%	10,230	1.6%	11,353	175	12,083	302	1.5%	12,083	302	12,083	302	1.5%	12,083	302	12,083	302	2.5%
Patient age 18-40	1,782,220	32,619	1.8%	2,091,030	1.6%	2,272,018	42,960	2,325,177	48,615	1.9%	2,325,177	48,615	2,325,177	48,615	1.9%	2,325,177	48,615	2,325,177	48,615	2.1%
Patient age 41-54	1,007,627	17,339	1.7%	1,220,963	1.5%	1,334,955	23,815	1,359,838	26,976	1.8%	1,359,838	26,976	1,359,838	26,976	1.8%	1,359,838	26,976	1,359,838	26,976	2.0%
Patient age 55+	774,593	15,281	2.0%	870,067	1.7%	937,063	19,145	965,339	21,640	2.0%	965,339	21,640	965,339	21,640	2.0%	965,339	21,640	965,339	21,640	2.2%
Patient age other	327,212	5,176	1.6%	354,369	1.5%	386,649	7,212	397,424	8,139	1.9%	397,424	8,139	397,424	8,139	1.9%	397,424	8,139	397,424	8,139	2.0%
Patient age 0-17	4,074	17	0.4%	3,544	2.4%	3,207	57	3,168	99	1.8%	3,168	99	3,168	99	1.8%	3,168	99	3,168	99	3.1%
Total TOPIRAMATE	1,513,906	38,034	2.5%	1,587,808	2.5%	1,718,400	50,441	1,797,558	57,168	2.9%	1,797,558	57,168	1,797,558	57,168	2.9%	1,797,558	57,168	1,797,558	57,168	3.2%
Patient age 0-17	82,045	222	0.3%	91,791	0.2%	101,598	212	103,894	315	0.2%	103,894	315	103,894	315	0.2%	103,894	315	103,894	315	0.3%
Patient age 12-17	18,773	13	0.1%	20,681	0.0%	22,193	37	21,883	13	0.2%	21,883	13	21,883	13	0.2%	21,883	13	21,883	13	0.1%
Patient age 18-54	63,272	209	0.3%	71,110	0.2%	79,406	175	82,011	302	0.2%	82,011	302	82,011	302	0.2%	82,011	302	82,011	302	0.4%
Patient age 18-40	1,129,307	32,619	2.9%	1,186,741	2.8%	1,281,423	42,960	1,335,700	48,615	3.4%	1,335,700	48,615	1,335,700	48,615	3.4%	1,335,700	48,615	1,335,700	48,615	3.6%
Patient age 41-54	571,540	17,339	3.0%	618,896	3.0%	677,968	23,815	704,971	26,976	3.5%	704,971	26,976	704,971	26,976	3.5%	704,971	26,976	704,971	26,976	3.8%
Patient age 55+	557,768	15,281	2.7%	567,846	2.6%	603,455	19,145	630,729	21,640	3.2%	630,729	21,640	630,729	21,640	3.2%	630,729	21,640	630,729	21,640	3.4%
Patient age other	297,504	5,176	1.7%	304,339	1.7%	331,052	7,212	352,438	8,139	2.2%	352,438	8,139	352,438	8,139	2.2%	352,438	8,139	352,438	8,139	2.3%
Patient age other	5,051	17	0.3%	4,937	1.7%	4,327	57	5,527	99	1.3%	5,527	99	5,527	99	1.3%	5,527	99	5,527	99	1.8%

±Claims from U.S. commercial, Medicare Part D, Cash and Medicaid plans. *Age is at first claim during calendar year

Source Wolters Kluwer Health's Source@ Lx. CPA tool Years 2006-2009, Extracted July 2010. File WKCPA 2010-1257 bupropion naltrexone patient counts by age per yr 2006-2009.xls

Figure 7



6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS's Vector One®: National (VONA)

IMS's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Wolters Kluwer SOURCE Lx®

Wolters Kluwer Health's Source® Lx database a longitudinal patient data source which capture adjudicated claims across the United States from a mix of prescription claims from commercial plans, Medicare Part D plans, Cash and Medicaid claims. The database contains approximately 4.8

billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

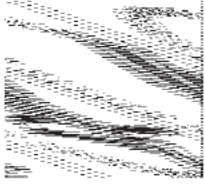
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRENDA V BORDERS-HEMPHILL
01/13/2012

HINA S MEHTA
01/13/2012
Drug use data cleared

LAURA A GOVERNALE
01/13/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff - Maternal Health Team Review

Date: December 20, 2011 **Date Consulted:** November 1, 2011

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD, DABT
Acting Team Leader Pediatric and Maternal Health Staff (Maternal Health}

Hari Cheryl Sachs, MD
Medical Team Leader, Pediatric and Maternal Health Staff (Pediatrics)

Lisa Mathis, MD
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: Qnexa (phentermine/topiramate) Controlled Release Capsules, NDA 22-580

Sponsor: Vivus, Inc.

Subject: PMHS Review of Qnexa Resubmission

Materials Reviewed:

- Vivus, Inc., Clinical review of Topiramate and PHEN/TPM Teratogenic Potential, submitted October 17, 2011

Consult Questions:

- Provide a summary of the risks associated with maternal weight and pregnancy and provide input on Vivus Inc.'s position regarding obesity as a teratogen.
- Provide consequences of oral facial clefts.

EXECUTIVE SUMMARY

This consult review provides the Pediatric and Maternal Health Staff responses to consult questions from the Division of Metabolic and Endocrine Product's (DMEP) for Qnexa (phentermine/topiramate) Controlled Release Capsules regarding:

- a summary of the risks associated with maternal weight and pregnancy and input on Vivus Inc.'s position regarding obesity as a teratogen;
- the consequences of oral facial clefts.

Vivus, Inc. submitted a study report titled, "Clinical Review of Topiramate and PHEN/TPM Teratogenic Potential," which presents the Sponsor's comprehensive review of published literature and available data on the potential teratogenic effects of topiramate as well as a recently conducted retrospective cohort study based on medical and prescription drug claims data. The Sponsor concludes that obesity is associated with major congenital malformations, including oral facial clefts. Furthermore, the Sponsor reports that no major congenital malformation or other adverse fetal outcome was observed in the thirty-four pregnancies that occurred during the Qnexa clinical trials. However, because of required monthly pregnancy testing in the clinical trials, no pregnancy was exposed to Qnexa for longer than 5 weeks gestation, a time period that is prior to the critical developmental window for the formation of the lip and palate.

The North American Anti-Epileptic Drug (NAAED) Pregnancy Registry submitted data to the Agency in 2010, which showed an increase in the risk of oral facial clefts in the offspring of mothers who had taken topiramate during the first trimester of pregnancy. This risk was also reported by the UK Epilepsy and Pregnancy Register.

A review of relevant literature by the Pediatric and Maternal Health Staff showed an association between maternal obesity and adverse pregnancy outcomes, with an increased risk of major congenital malformations, including oral facial clefts in offspring. Obese women are also prone to develop overt diabetes and chronic hypertension and neonates of obese women tend to be large for gestational age (macrosomic). These pregnancies have a higher incidence of birth injuries, premature delivery, and late fetal deaths. Some researchers hypothesize that malformations that occur as a result of maternal diabetes are the result of uncontrolled hyperglycemia. Many obese women have overt diabetes or some degree of insulin resistance. The causal mechanism for the association observed between obesity and major congenital malformations, including oral facial clefts, is not known but may be related to the severe metabolic and hormonal alterations including hyperglycemia, diabetes, elevated insulin levels, elevated estrogen levels, and/or nutritional deficits from dieting or poor quality diets.

The Pediatric and Maternal Health Staff does not agree with the sponsor's assertion that that weight loss from use of Qnexa may prevent the number of major congenital malformations associated with obesity, and that the number of these major congenital anomalies prevented should be as great, or greater than the number of oral facial clefts likely to be caused by topiramate. Such an assertion is speculative and not supported by available data. Maternal exposure to Qnexa has the potential to increase the occurrence of oral facial clefts in offspring over the current background rate, without the added risk from obesity. The association between

maternal obesity with topiramate exposure and an increased risk of oral facial clefts in offspring compared to maternal obesity without topiramate exposure has not been examined. Larger scale studies are needed to accurately and adequately define the risk of maternal topiramate use and oral facial clefts in offspring; the risk of maternal obesity and oral facial clefts in offspring; and the risk of maternal obesity with topiramate use and oral facial clefts in offspring.

Oral facial clefts are not trivial birth defects for the affected child or family. Maternal exposure to Qnexa has the potential to increase the occurrence of oral facial clefts in offspring over the current background rate of approximately 17/10,000 live births in the U.S. While oral facial clefts are surgically repairable, affected children generally face treatment into adulthood, including multiple surgeries, feeding assistance, speech therapy, and dental and orthodontic treatments. Many of these children have repeated ear infections and are at risk for hearing problems due to these infections, usually resulting from eustachian tube dysfunction. Many children and families face emotional and psychosocial problems due the appearance of the oral facial cleft, especially if the cleft is visible. Surgery can never eradicate the facial appearance in a child with an oral facial cleft which often leads to alterations in self-confidence and body image.

INTRODUCTION

On October 17, 2011, Vivus, Inc. submitted a Complete Response Submission for Qnexa (phentermine/topiramate) Controlled Release Capsules, NDA 22-580, in response to the October 28, 2010, Complete Response Letter issued by the Agency. Qnexa is a fixed-dose combination of immediate-release phentermine hydrochloride beads and modified-release topiramate beads studied in the once daily doses of 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg, and is proposed 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 ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight patients ($\text{BMI} \geq 27 \text{ kg/m}^2$) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).¹

The Qnexa Complete Response Letter was issued for clinical concerns regarding teratogenicity with topiramate and cardiovascular safety with Qnexa. Vivus, Inc. Complete Response Submission contains a study report titled, “Clinical Review of Topiramate and PHEN/TPM Teratogenic Potential,” which presents the Sponsor’s comprehensive review of published literature and available data on the potential teratogenic effects of topiramate as well as a recently conducted retrospective cohort study based on medical and prescription drug claims data. Vivus, Inc. summarized findings that topiramate is associated with an increased risk of oral facial clefts and that obesity is associated with major congenital malformations, including oral facial clefts (see table 12 below). Vivus, Inc. asserts that weight loss from Qnexa use may prevent the number of major congenital malformations associated with obesity, and the number of these major congenital anomalies prevented should be as great, or greater than the number of oral facial clefts likely to be caused by topiramate.²

¹ See draft Qnexa labeling, submitted October 17, 2011

² Vivus, Inc., Clinical review of Topiramate and PHEN/TPM Teratogenic Potential, submitted October 17, 2011

Table 12. Excess Risk of Oral Clefts and MCMs due to Topiramate Exposure and Obesity

	Excess Oral Clefts due to Topiramate	Excess MCMs due to Obesity
Risk Level	5x	2x
Background Prevalence	0.15%	2.5%
Expected Prevalence with TPM/Obesity	0.75%	5.0%
Risk Difference due to TPM/Obesity	0.6%	2.5%
Excess Malformations/10,000 Pregnancies due to TPM/Obesity	60	250

Reviewer Comment: The Sponsor compares the excess risk of oral clefts due to topiramate to the excess risk of all major congenital malformations due to maternal obesity in the above table. The appropriate comparison should have been a sub analysis showing the excess risk of oral clefts due to topiramate to the excess risk of oral clefts due to maternal obesity. The Sponsor's assertion that weight loss from Qnexa use may prevent the number of major congenital malformations associated with obesity, and the number of these major congenital anomalies prevented should be the number of these major congenital anomalies prevented should be as great, or greater than the number of oral facial clefts likely to be caused by topiramate is speculative and not supported by available data.

The Division of Endocrine and Metabolic Products consulted the Pediatric and Maternal health Staff on November 1, 2011, to 1) provide a summary of the risks associated with maternal weight and pregnancy, and provide input on the Sponsor's position regarding obesity as a teratogen; and, 2) provide consequences of oral facial clefts, as 34 women became pregnant while participating in Qnexa clinical trials despite a study requirement for females of childbearing potential to use two forms of contraception while on study drug. The Qnexa New Drug Application will be discussed at an Endocrinology and Metabolic Drugs Advisory Committee Meeting on February 22, 2012

This review will focus mainly on an overview of the association between maternal obesity and an increased risk for oral facial clefts and a general discussion on oral facial clefts.

BACKGROUND

Topiramate and phentermine are both FDA-approved drug products. Topiramate, an anti-epileptic drug (AED) is approved for epilepsy and migraine prophylaxis and is classified as a pregnancy category D drug for use in pregnancy³. Pregnancy exposure data sent to the Agency in 2010 from the North American Anti-Epileptic Drug (NAAED) Pregnancy Registry⁴ indicated an increased risk for the development of cleft lip and/or cleft palate (oral facial clefts) in infants born to women treated with topiramate (Topamax and generic products) during pregnancy. The prevalence of oral facial clefts was 1.2% compared to a prevalence of 0.39% - 0.46% in infants exposed to other AEDs, and a prevalence of 0.12% in infants of mothers without epilepsy or treatment with other AEDs. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral facial clefts in the United States and found a similar

³ See Appendix A for a summary of pregnancy category classifications

⁴ The NAAED pregnancy registry is designed to obtain and publish information on the frequency of major malformations among infants whose mothers have taken one or more AEDs for any medical condition.

background rate of 0.17%. The relative risk of oral facial clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval, 3.6 – 25.7) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral facial clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral facial clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%.⁵

Phentermine, a sympathomimetic amine anorectic is the most commonly prescribed medication for short term use for the treatment of obesity in the U.S.⁶ All phentermine products labeling are currently being re-classified from a pregnancy category I (no animal or human data) to a pregnancy category X (no benefit for use in pregnancy and potential risks) because of the current clinical guidelines⁷ for weight gain during pregnancy, and recommendation against weight loss, even in obese women. As an example, the Suprenza (phentermine hydrochloride) oral disintegrating tablet pregnancy labeling is noted below

Pregnancy

Pregnancy Category X

Suprenza is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to obligatory weight gain that occurs in maternal tissues during pregnancy. Phentermine has pharmacologic activity similar to amphetamine (d- and d/l-amphetamine) [see Clinical Pharmacology (12.1)]. Animal reproduction studies have not been conducted with phentermine. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

No teratogenicity was observed in a small series of human pregnancies exposed to phentermine.⁸ Phentermine is found in combination with topiramate in Qnexa. Phentermine has pharmacologic activity similar to amphetamines so it is important to consider potential amphetamine vascular side effects, including vasoconstriction and a rise in blood pressure, on a pregnancy. There have been no animal or human studies conducted with phentermine to assess these effects but the effect of methamphetamine was studied in pregnant sheep.^{9 10} These studies demonstrated that methamphetamine readily crossed the placenta caused an elevation in maternal and fetal blood pressure, a decrease in fetal oxyhemoglobin saturation and pH, as well as a transient increase in umbilical vascular resistance, and a decrease in uterine blood flow accompanying these changes.

⁵ See Current Approved Topamax labeling, July 15, 2011

⁶ Hendricks EJ, Rothman RB, Greenaw FL. How physician obesity specialists use drugs to treat obesity. *Obesity* 2009 Sep;17(9):1730-5

⁷ See Appendix B for the current Institute of Medicine Pregnancy Weight Gain Guidelines

⁸ See REPROTOX[®] REPROTOX[®] is a subscription information system on environmental hazards to human pregnancy, reproduction and development developed by the Reproductive Toxicology Center for its members. REPROTOX contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development. Available through MicroMedex.

⁹ Stek A, Baker R, et al. Fetal responses to maternal and fetal methamphetamine in sheep. *Amer J Obstet and Gyn* 1995; Nov;173(5):1592-1598.

¹⁰ Stek A, Fisher B, et al. Fetal responses to maternal and fetal methamphetamine in the pregnant sheep. *Amer J Obesity and Gyn* 1993; Oct;169(4):888-897

Thirty-four pregnancies¹¹ occurred during the Qnexa clinical trials. No major, structural congenital malformations or other adverse fetal outcomes were identified in the resultant live births. However, because of required monthly pregnancy testing in the clinical trials, no pregnancy was exposed to Qnexa for longer than 5 weeks gestation. Subjects were discontinued prior to the critical developmental window for lip and palate formation.

Obesity and Oral Facial Clefts

Maternal obesity, diabetes, and other metabolic disorders have been associated with major congenital malformations, including oral-facial clefts. Several researchers have examined the association between maternal weight and major congenital malformations in offspring.

Maternal obesity is associated with many pregnancy complications including gestational diabetes and hypertension. Allen, et al,¹² reviewed medical literature published between 1990 and 2005 relating to pre-existing and gestational diabetes and fetal abnormalities. The author's objective was to provide guidelines to optimize the prevention and diagnosis of fetal abnormalities in women with diabetes and to identify areas specific to congenital anomalies and diabetes requiring further research. The authors found that experimental animal studies suggest that hyperglycemia is the major risk factor in diabetic pregnancies, but other diabetes-related factors may also affect fetal outcomes.. The risk of congenital anomalies was found to be increased in obese women with diabetes, but a healthy diet and regular exercise may help optimize pre-pregnancy weight and reduce the risk of congenital anomalies.

Correa, et al,¹³ conducted a multi-center case-control study of mothers of infants born with and without birth defects using the NBDPN to examine associations between diabetes mellitus type 1 and 2) and 39 birth defects. Pre-gestational diabetes was associated significantly with both cardiac and non-cardiac defects. An increased risk in isolated cleft palate (OR 1.80; 95% CI, 0.67-4.87), and cleft lip, with or without cleft palate (OR 2.92; 95% CI, 1.45-5.87) was observed. Gestational diabetes was associated with fewer birth defects; however there was an increased risk of isolated cleft palate (OR 1.54; 95% CI, 1.01-2.37), and cleft lip, with or without cleft palate (OR1.45; 95% CI, 1.03-2.04). These associations occurring with gestational diabetes were generally limited to offspring of women with pre-pregnancy BMI ≥ 25.0 . The authors concluded that these findings support the hypothesis that the embryopathy associated with diabetes mellitus is non-specific and that complex, underlying metabolic disorders associated with diabetes mellitus increase the likelihood that different signal transduction pathways and morphogenic processes may be disturbed. The findings highlight the importance of identifying and implementing effective detection, control and prevention strategies for impaired glucose tolerance in women of reproductive potential.

Stott-Miller, et al,¹⁴ conducted a population-based case-control study using the Washington State birth certificate and hospitalization data collected from 1987-2005, to evaluate whether infants born to obese or diabetic women at a higher risk for isolated oral facial clefting. Infants born to

¹¹ See Qnexa Clinical Study Report, OB-302 11/1/2007 – 5/19/09

¹² Allen V, Armson B, et al. Teratogenicity associated with pre-existing and gestational diabetes. J Obstetric Gyn Can 2007; 29(11):927-944

¹³ Correa A, Gilboa S, et al. Diabetes mellitus and birth defects. Amer J Obstet & Gyn 2008;199-237

¹⁴ Stott-Miller M, Heike C, et al. Increased risk of orofacial clefts with maternal obesity: case-control study and Monte Carlo bias analysis. Ped and Perinat Epidem 2010; 24:501-512

obese women had a small increase risk of isolated oral facial cleft (OR 1.26; 95% CI, 1.03-1.55) compared to normal body mass index weight women. The associations were similar cleft lip with or without cleft palate and cleft palate alone. The results for diabetic women were inconsistent, probably due to too few cases of women with pre-existing diabetes in this study. An increased risk of diabetes and glucose intolerance is associated with obesity, and excess adiposity may involve metabolic abnormalities similar to diabetes; therefore, the biological mechanisms that result in increased rates of congenital anomalies in diabetic women may be similar for obese women. The authors concluded that their findings with maternal obesity and an increased risk of oral facial clefts was similar to findings from other studies and that obesity is a modifiable risk factor for oral facial clefts in offspring.

Mandal D, et al,¹⁵ conducted a longitudinal prospective study in 422 pre-pregnant obese women with an equal number of non-obese pregnant women as controls to analyze whether obese women have an increased risk of pregnancy complications and adverse fetal outcomes. The authors found that obese women were prone to develop overt diabetes and chronic hypertension. Neonates of obese women were large for gestational age, had a higher incidence of birth injuries, premature delivery, late fetal deaths, and congenital malformations, particularly spina bifida, cleft lip, cleft palate, and heart defects.

Rankin, et al¹⁶ conducted a cohort study using prospectively collected data to investigate the association between maternal body mass index (BMI) and major structural congenital malformations. They found an overall increased risk of congenital anomalies in both women whose BMI was greater (obese) and women whose BMI was less (underweight), compared to women with the recommended BMI. Maternal obesity was associated with an increase risk of oral facial clefts (OR 1.76; 95% CI, 0.84-3.66), cleft lip (OR 3.71; 95 % CI, 1.05-13.10), and cleft lip and palate (OR 1.48; 95% CI, 0.46-4.76). In comparison maternal underweight was also associated with an increased risk of oral facial clefts (OR 1.84; 95% CI, 0.55-6.25). The authors concluded that women should be made aware of these risks and encouraged to optimize their weight prior to a pregnancy.

Stothard, et al¹⁷ conducted an observational study using available medical literature databases to look for evidence of an association between maternal obesity and some congenital anomalies. Pooled odds ratios (ORs) for overweight and obesity were calculated for 16 and 15 anomaly groups or subtypes, respectively. Compared with mothers of recommended BMI, obese mothers were at increased odds of pregnancies affected by several congenital anomalies, including cleft palate (OR 1.23; 95% CI, 1.03-1.47), cleft lip and palate (OR 1.20; 95% CI, 1.03-1.40). The authors concluded that maternal obesity is associated with an increased risk of a range of structural anomalies, although the absolute risk is likely to be small. Further studies are needed to confirm whether maternal overweight is associated with an increased risk of major congenital anomalies.

¹⁵ Mandal D, Manda S, et al. Maternal obesity and pregnancy outcome: a prospective analysis. J Assoc Physicians India 2011; 59:486-489

¹⁶ Rankin J, Tennant P, et al. Maternal body mass index and congenital anomaly risk: a cohort study. 2010 Inter J Obesity 2010; 34:1371-1380

¹⁷ Stothard K, Tennant P. Maternal overweight and obesity and the risk of congenital anomalies: a systemic review and meta-analysis. JAMA 2009; 301(6): 636-650

To address the inconsistency of data regarding the influence of maternal obesity on oral clefts, Villamor E et al,¹⁸ conducted a population-based retrospective cohort study among 300,510 women who had their first two consecutive singleton-births between 1992 and 2004, as recorded in the Swedish Medical Birth Registry to investigate whether increases in maternal weight before pregnancy are related to the risk of oral clefts. The authors found that among women whose second pre-pregnancy BMI was ≥ 3 units higher than their first pregnancy BMI, the adjusted risk of isolated cleft palate was higher (OR 2.3; 95% CI, 1.4-4.0) compared to women whose pre-pregnancy BMI did not change substantially. An association with pre-pregnancy BMI increase and isolated cleft lip was not found. The authors did find that the prevalence of isolated cleft palate per 1000 live births increased linearly with the length of the inter-pregnancy interval, from 0.3 in women with inter-pregnancy intervals ≤ 12 months, to 0.9 in women with inter-pregnancy intervals ≥ 48 months. The authors concluded that high pre-pregnancy weight gain and long inter-pregnancy intervals appear to be associated with an increased risk of cleft palate.

Waller, et al¹⁹ conducted a case-control study to describe the relationship between maternal obesity (BMI ≥ 30.0), overweight (BMI 25.0 to < 30.0), and underweight (BMI < 18.5) status, and 16 categories of structural birth defects. The investigators used the National Birth Defects Prevention Network (NBDPN), an ongoing 8-state, multi-site, case-control study for their research. An increased risk for cleft palate and cleft lip/palate was observed in both obese and underweight mothers, but not in overweight mothers. Mothers of offspring with spina bifida, heart defects, diaphragmatic hernia, and omphalocele were more likely to be obese than the mothers of controls, while mothers of offspring with gastroschisis were less likely to be obese than the mothers of controls.

Watkins, et al,²⁰ conducted a population-based, case-control study of several selected major birth defects using data from the Atlanta Birth Defects Risk Factor Surveillance Study to explore the relationship between maternal pre-pregnancy obesity and overweight and several birth defects and compared the findings with those of previous studies. Cases with preexisting diabetes were excluded from the analysis. This study confirmed the previously established association between spina bifida and pre-pregnancy maternal obesity, as well as finding an association for omphalocele, heart defects, and multiple anomalies among infants of obese mothers. The odds ratio for oral facial clefts in infants of obese mothers in this study was found to be 0.8; 95% CI, 0.4-1.8). The authors report the causal mechanism for the association observed between obesity and major congenital malformations is not known but may be related to severe metabolic and hormonal alterations including hyperglycemia, diabetes, elevated insulin levels, elevated estrogen levels, and/or nutritional deficits from dieting or poor quality diets.

Oral facial Clefts

The National Birth Defects Prevention Network (NBDPN)²¹ reports that oral facial clefts (cleft lip and/or cleft palate) occur at an estimated prevalence rate of 17/10,000 live births in the U.S.

¹⁸ Villamor E, Sparen P, Cnattingus S. Risk of oral clefts in relation to prepregnancy weight change and interpregnancy interval. *Amer J Epidemiol* 2008;167:1305-1311

¹⁹ Waller K, Shaw G, Rasmussen S, et al. Pregnancy obesity as a risk factor for structural birth defects. *Arch Pediatr Adolesc Med* 2007; 161(8):745-750

²⁰ Watkins M, Rasmussen S, et al. Maternal obesity and risk for birth defects. *Pediatrics* 2003; 111(5):1151-1158

²¹ The National Birth Defects Prevention Network collects state-specific birth defects surveillance data for annual publication and prevalence estimates and collaborative research projects.

Cleft palate without cleft lip has an estimated prevalence rate of 6.4/10,000 live births (approximately 2,651 babies per year) and cleft lip with and without cleft palate has an estimated prevalence rate of 10.6/10,000 live births (approximately 4,437 babies per year). Cleft lip with and without cleft palate is the second most common birth defect in the U.S.; however, the prevalence rate varies with geography, ethnicity, and socio-economic status.^{22,23} The majority of oral facial clefts, approximately 70 percent, occur in isolation and are not associated with other congenital malformations. Visible clefts (cleft lip) are more common in males, while non-visible clefts (cleft palate) are more common in females.²⁴

The lip is formed between the beginning of the fifth week to the seventh week of gestation and the palate is formed between the beginning of the sixth week through the ninth week of gestation.²⁵ Depending on the degree of involvement, cleft lips can occur unilaterally or bilaterally and may extend to include the nose. Cleft palates can involve all or part of the palate. In more severe cases cleft lip and palate occur together.

Research into the etiology of oral facial clefts have looked at associations between oral clefts and maternal smoking, maternal alcohol use, maternal nutrition/vitamin supplementation maternal metabolism including diabetes, obesity, and other metabolic disorders, as well as genetic factors predisposing for oral facial clefts. A consistent association between maternal smoking and oral facial clefts has been demonstrated, with an increased risk of both cleft lip and palate and isolated cleft palate. The population-attributable risk is reported as high as 20 percent, but may be underestimated because passive exposure to cigarette smoke has not been assessed in most studies.^{26,27,28} The association with maternal alcohol use and isolated oral facial clefts is less certain, with some studies showing an association and others not showing an association.²⁹ In contrast, a meta-analysis completed in 2008,³⁰ showed maternal use of multivitamin supplements in early pregnancy was associated with a 25 percent reduction in birth prevalence of oral facial clefts; however, it cannot be determined which nutrients in the multivitamins are protective, and whether or not women that use multivitamins also have other healthy behaviors. An association between maternal metabolic disorders including diabetes and obesity has been observed in numerous studies (for further background see information under the previous section, Obesity and Oral Facial Clefts).

²² Parker S, Mai C, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth def Research (Part A): Clin and Molec Teratol* 2010; 88:108-1016

²³ Mossey P, Shaw W, et al. Global oral health inequities: challenges in the prevention and management of oral facial clefts and potential solutions. *Adv Dent Res* 2011; 23(2):246-258

²⁴ Siversten A, Wilcox A, et al. Prevalence of major anatomic variations in oral clefts. *Plastic and Reconstructive Surgery* 2008 121:587-595

²⁵ Sadler T. *Langman's Medical Embryology*, 6th Edition. Williams & Wilkins, Baltimore, MD, 1980

²⁶ Mossey P, Shaw W, et al. Global oral health inequities: challenges in the prevention and management of oral facial clefts and potential solutions. *Adv Dent Res* 2011; 23(2):246-258

²⁷ Little J, Carddy A, et al. Smoking and oral facial clefts; a United Kingdom-bases case-control study. *Cleft palate Craniofac J* 2004a; 41:381-386

²⁸ Honein M, Rasmussen S, et al. Maternal smoking and environmental tobacco smoke exposure and the risk of oral facial clefts. *Epidemiology* 2007; 18:226-233

²⁹ Mossey P, Shaw W, et al. Global oral health inequities: challenges in the prevention and management of oral facial clefts and potential solutions. *Adv Dent Res* 2011; 23(2):246-258

³⁰ Johnson C, Little J. Folate intake, markers of folate status and oral facial clefts: is the evidence converging. *Int J Epidem* 2008; 37:1041-1058

The wide spectrum of oral facial clefts and the care of a child with an oral facial cleft require a multidisciplinary team approach, is long term, and must be individually tailored.³¹ The treatment of oral facial clefts generally extends into adulthood, requiring multiple surgeries, feeding assistance, speech therapy, dental and orthodontic treatments. Children with oral facial clefts have an increased risk for feeding problems, speech and learning disabilities, an increased risk for ear infections, and persistent middle ear effusions due to insufficient eustachian tube function. Psychosocial support and counseling is required for both the family and child starting immediately at birth. The multidisciplinary team can include plastic surgeons, otolaryngologists, dentists, orthodontists, speech and language therapists, social workers, and specialty nurses. Although oral facial clefts can be diagnosed during pregnancy during a routine ultrasound; many oral facial clefts are diagnosed after birth. Diagnosis may be delayed for minor clefts, including a submucous cleft palate and bifid uvula.³²

Oral facial clefts can be surgically repaired and often require multiple surgeries. In addition to the general surgical risks of bleeding, infection, and death specific post-operative complications can include oro-nasal fistula development and velopharyngeal insufficiency following primary cleft palate repair. Inman, et al,³³ reviewed primary cleft palate surgery in 148 children who had undergone cleft lip or palate surgery at a hospital in the U.K. The authors found a 4.7% rate of oro-nasal fistula development requiring additional surgical closure, and a 26.4% rate of velopharyngeal insufficiency requiring a subsequent pharyngoplasty with 16% of these patients with a unilateral cleft lip and palate versus 29.2% of patients with a solitary cleft palate requiring secondary surgery. Speech therapy in follow-up clinics demonstrated that 14.9% of these children had a degree of hyper-nasality in their speech.

The Clinical Standards Advisory Group (CSAG) Cleft Lip and Palate Study³⁴ is a national study of care and outcomes in children born with a unilateral cleft lip and palate conducted over a 15-month period in the U.K. Two cohorts of children (n= 326 5 year olds and n= 321 12 year olds) were examined. The following outcomes were assessed: dental arch relationship, skeletal relationship, quality of alveolar bone graft, oral health, psychosocial status, difficulties attending cleft clinics and parent satisfaction. Dental arch relationship was identified as being poor or very poor in 37% of 5 year olds and 39% of 12 year olds. Seventy percent of all children had a skeletal Class III malocclusion (the lower front teeth are more prominent than the upper front teeth). The quality of the alveolar bone graft was assessed in 157 children, of which only 58% of the bone grafts were shown to be successful. Oral health was evaluated and 40% of 5 year olds and 20% of 12 year olds required treatment for dental caries and 39% of 5 year olds and 10% of 12 year olds were found to have a persistent oral fistula which was causing problems with feeding and speech. Psychosocial issues were assessed with 19% of parents of 5 year olds and 28% of parents of 12 year olds reporting that their child's self confidence had been affected by the cleft. In addition 33% of 12 year olds reported current teasing about the cleft, with 25% of these children worried by the teasing.

³¹ Fisher D, Sommerlad B. Cleft lip, cleft palate, and velopharyngeal insufficiency. *Plastic and Reconst Surg* 2011; 128(4):342e-360e

³² Facts about cleft lip and cleft palate. www.cdc.gov/ncbddd/birthdefects/cleftlip.html

³³ Inman D, Thomas P, et al. Oro-nasal fistula development and velopharyngeal insufficiency following primary cleft palate surgery- an audit of 148 children born between 1985 and 1997. *Brit J Plast Surg* 2005; 58:1051-1054

³⁴ Sandy J, Williams A, et al. The clinical standards advisory group (CSAG) Cleft lip and palate study. *Brit J of Orthodontics* 1998; 25:21-30

Reid, et al,³⁵ conducted a prospective, longitudinal study in 62 babies to examine the natural history of feeding skills in a cohort of babies with cleft conditions. Feeding ability, oral motor function, and feeding efficiency were assessed. Poor feeding skills are common in infants with cleft palate or cleft lip and palate; especially in those with larger cleft defects. These infants usually require the use of special nipples and feeding equipment. Oral motor dysfunction causing nasal regurgitation was commonly observed in infants with poor feeding skills. The authors concluded that feeding problems with cleft palate or cleft lip and palate may require treatment beyond infancy.

Oral facial clefts impact the parent-child relationship. Murray, et al,³⁶ report that many parents demonstrate shock and distress when they first see their oral facial cleft-affected infant after birth. This reaction can affect long-term parental-infant attachment. Interventions to facilitate parent-child interactions should be instituted, as children with oral facial clefts are at increased risk for socio-emotional and cognitive disorders during infancy and childhood.

Kuttenberger, et al,³⁷ conducted a retrospective, cross-sectional survey of 105 families who attended a multidisciplinary cleft clinic. The study confirmed the importance of initial parental counseling due to the psychosocial situation of having a child with an oral facial cleft. Parents may initially feel shocked, disappointed, helpless and distressed after having a child with an oral facial cleft; these emotions can be present regardless of prenatal knowledge of the cleft. Initial counseling by a cleft team is critical immediately after birth to provide knowledge, support, and encouragement for the parents. This initial counseling can have a positive effect on the development of parent adaptability to their child's malformation.

Jocelyn, et al,³⁸ conducted a prospective, longitudinal study to compare a group of children with cleft lip and palate to a group of non-cleft children matched control children on measures of cognitive development, speech and language abilities, and audiologic status, at 12 and 24 months of age. Instruments and measurements used included the Bayley Scales of Infant Development, the Receptive-Expressive Emergent Language Scale, the Sequenced Inventory of Communication development-Revised, the Preschool Language Scale-Revised, the mean length of utterance, audiometric evaluation, and impedance screening. Children with cleft lip and palate had lower mental and psychomotor development, lower language expression, and higher incidence of tympanogram abnormalities or ventilation tubes placement. In addition a relationship was shown between hearing status at 12 months and comprehension and expressive language scores at 24 months. Children with cleft lips had significantly lower scores on tests of cognition, comprehension, and expressive language abilities, as well as having a higher frequency of middle-ear disease and ventilation tubes placed, although no significant difference in hearing sensitivity was seen compared to the matched controls. The authors concluded that

³⁵ Reid J, Kilpatrick N, et al. A prospective, longitudinal study of feeding skills in a cohort of babies with cleft conditions. *Cleft Palate- Craniofacial J* 2006; 43(6):702-709

³⁶ Murray L, Hentges F, et al. The effect of cleft lip and palate, and the timing of lip repair on mother-infant interactions and infant development. *J of child Psychology and Psychiatry* 2008;49(2):115-123

³⁷ Kuttenberger J, Ohmer M, et al. Initial counseling for cleft lip and palate: parents' evaluation, needs and expectations. *Int J Oral Maxillofac Surg* 2010; 39:214-220

³⁸ Jocelyn L, Penko M, et al. Cognition, communication and hearing in young children with cleft lip and palate and in control children; a longitudinal study. *Pediatrics* 1996; 97:529-534

early detection and intervention for speech and language delays is very important for children born with oral facial clefts.

Marcussen,³⁹ investigated the quality of life, satisfaction with treatment, prevalence of temporomandibular disorders, psychosocial distress, and occlusal stability in a treated group 68 adults with treated cleft lip and palate, comparing with a gender- and age-matched group with no clefts. The subjects answered a multidimensional, self-report, standardized questionnaire regarding psychological and somatic conditions and underwent a clinical examination and an evaluation of any occlusion. Overall aspects such as well-being and social life were affected by having a treated cleft; however, overall quality of life was reported as good by subjects with treated cleft lip and palate. Persistence of temporomandibular disorders was observed in these adults as well as occlusal instability, with many patients wanting further surgeries to improve their appearance. The author concluded that the cleft lip and palate adults in this study seemed to be psychosocially well adjusted to their disability.

Feragen, et al,⁴⁰ investigated the role of social acceptance in self-perception of appearance and depressive symptoms, comparing adolescent males with a visible oral facial cleft to those with a non-visible cleft, and with a comparison group without any cleft. The authors found that close friendships and social acceptance may have a role in preventing and treating appearance-related distress in children and adolescents that look different. Interventions should be directed at developing social competence in children with oral facial clefts, improve their social confidence, and strengthen satisfaction with self-appearance.

DISCUSSION

Obesity presents a significant public health problem in the U.S. with a rapid increase in obesity prevalence in the last two decades. In 2007 - 2008, the prevalence of obesity in U.S. women was 35.5%.⁴² In 2003 – 2004, approximately 30% of U.S. women ages 20 - 39 years were obese based on data from the National Health and Nutrition Examination Survey.⁴³ Obesity has a negative impact on a woman's reproductive health including polycystic ovarian syndrome, menstrual irregularities, difficulty conceiving, and a possible higher risk for repetitive early spontaneous abortions.⁴⁴ Excessive weight gain during pregnancy can lead to an increased risk of hypertension, maternal insulin resistance and gestational diabetes which can lead to fetal hyperglycemia and increased adiposity. Neonates of obese women tend to be large for gestational age (macrosomic). In addition, these babies have a higher risk for childhood obesity

³⁹ Marcussen A. Adult patients with treated complete cleft lip and palate. Methodological and clinical studies. Swedish Dental J Supple 2001;145:1-57

⁴⁰ Feragen K, Kvaalem I, et al. Adolescents with and without facial difference: The role of friendships and social acceptance in perceptions of appearance and emotional resilience. Body Image 2010; 7:271-279

⁴¹ Warschausky s, Kay J, et al. Health-related quality of life in children with craniofacial anomalies. Plastic and Reconstructive Surgery 2001; 100(2):409-414

⁴² Flegal K, Carroll M, et al. Prevalence and trends in obesity in US adult, 1999-2008. JAMA 2010 Jan;303(3):235-241

⁴³ Ogden C, Carroll M, et al. Prevalence of overweight and obesity in the US, 1999-2004. JAMA 2006;295:1549-1555

⁴⁴ Brown K, Apuzzia J, WeissG. Maternal obesity and associated reproductive consequences. Women's health 2010; 6(2):197-203

and accompanying metabolic sequelae.⁴⁵ Maternal obesity is also associated a higher incidence of birth injuries, premature delivery, late fetal deaths, and congenital malformations, particularly spina bifida, cleft lip, cleft palate, and heart defects.⁴⁶ Available data on the background incidence for congenital malformations suggest that major birth defects occur in 2-4% of the U.S. general population.⁴⁷

Most studies conducted to investigate the association between pre-pregnancy obesity and an increased risk of major structural congenital malformations have shown an association, including a risk for oral facial clefts; however, the magnitude of risk varies between studies. The majority of the studies did not adjust for diabetes or other metabolic disorders in obese women. Of note a few studies showed similar findings of an increased risk of oral facial clefts in offspring of women who were underweight pre-pregnancy, suggesting the importance of normal pre-pregnancy weight. Pregnancy itself induces metabolic alterations, including adiposity and insulin resistance, and these alterations are an adaptive response to allow a more efficient transfer of fuels across the placenta to the fetus.

Some research studies suggest that hyperglycemia is the major risk factor in diabetic pregnancies.⁴⁸ The risk of major congenital malformations is increased in obese women with diabetes, and diabetes occurs frequently in the obese population. One group of researchers concluded that the embryopathy associated with diabetes is non-specific, and that complex, underlying metabolic disorders associated with diabetes increase the likelihood that different signal transduction pathways and morphogenic processes may be disturbed.⁴⁹ Other authors report that the causal mechanism for the association observed between obesity and major congenital malformations is not known but may be related to the severe metabolic and hormonal alterations including hyperglycemia, diabetes, elevated insulin levels, elevated estrogen levels, and/or nutritional deficits from dieting or poor quality diets.⁵⁰ The majority of researchers emphasized the importance of identifying and implementing effective detection, control and prevention strategies for impaired glucose tolerance in women of reproductive potential. Most of the researchers agreed that optimizing weight pre-pregnancy through a healthy diet and regular exercise may reduce, but not eliminate the risk of major congenital malformations.

The North American Anti-Epileptic Drug (NAAED) Pregnancy Registry and the UK Epilepsy and Pregnancy Register both reported an increased risk of oral clefts in offspring with maternal use of topiramate during the first trimester of pregnancy. Other epidemiologic studies are currently examining the association between maternal topiramate use and an increased risk for oral facial clefts in offspring.

⁴⁵ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: <http://nap.edu/catalog/12584.htm>

⁴⁶ Mandal D, Manda S, et al. Maternal obesity and pregnancy outcome: a prospective analysis. *J Assoc Physicians India* 2011; 59:486-489

⁴⁷ Rynn L, Cragan J, Correa A. Update on Overall Prevalence of Major Birth Defects-Atlanta, Georgia, 1978-2005. *CDC MMWR* January 11, 2008/57(01);1-5.

⁴⁸ Allen V, Armson B, et al. Teratogenicity associated with pre-existing and gestational diabetes. *J Obstet Gyn Can* 2007; 29(11):927-944

⁴⁹ Allen V, Armson B, et al. Teratogenicity associated with pre-existing and gestational diabetes. *J Obstet Gyn Can* 2007; 29(11):927-944

⁵⁰ Watkins M, Rasmussen S, et al. Maternal obesity and risk for birth defects. *Pediatrics* 2003; 111(5):1151-1158

Oral facial clefts are the second most common birth defect in the U.S. and the majority of these clefts occur in isolation. There is a wide spectrum of oral facial cleft deformities and the care of a child with an oral facial cleft deformity and family requires a multidisciplinary team approach, is long term, and must be individually tailored to the specific oral facial cleft defect.⁵¹ Children with oral facial clefts have an increased risk for feeding problems, speech and learning disabilities, and an increased risk for ear infections, and persistent middle ear effusions due to insufficient eustachian tube function. Psychological support and counseling is required for both the child and family, starting at birth. Children with oral facial clefts may face problems with self-confidence, body image, and social competence, and many of these children are subjected to teasing and bullying because of their different facial appearance.⁵²

CONCLUSIONS

Maternal obesity is increasing in prevalence in the U.S. and is associated with an increase risk for adverse pregnancy outcomes, including an increased risk of oral facial clefts in offspring. The magnitude of this risk has not been clearly defined; however, most small studies that examined the association between maternal obesity and the occurrence of oral facial clefts in offspring did find an increased risk for these malformations. The causal mechanism for the association observed between obesity and major congenital malformations, including oral facial clefts is not known but may be related to the severe metabolic and hormonal alterations including hyperglycemia, diabetes, elevated insulin levels, elevated estrogen levels, and/or nutritional deficits from dieting or poor quality diets.

Topiramate exposure in the first trimester of pregnancy has been associated with an increased risk for oral facial clefts by large registry databases (NAAED and UK Epilepsy and Pregnancy Register). While there is no data currently available on the exposure of Qnexa (phentermine/topiramate) during the first trimester critical developmental window for lip and palate formation, it is plausible to assume an increased risk from exposure to this drug in obese pregnant women. Furthermore, the Pediatric and Maternal Health Staff does not agree with the sponsor's assertion that that weight loss from use of Qnexa, which contains topiramate, may prevent the number of major congenital malformations associated with obesity, and the number of these major congenital anomalies prevented should be as great, or greater than the number of oral facial clefts likely to be caused by topiramate. Such an assertion is speculative and not supported by data. Maternal exposure to Qnexa has the potential to increase the occurrence of oral facial clefts in offspring over the current background rate, without the added risk from obesity.

Oral facial clefts are surgically repairable; however, affected children generally face treatment and therapy into adulthood. Oral facial clefts are not a trivial birth defect for the affected child or family. Surgery can never eradicate the facial appearance in a child with an oral facial cleft, often leading to alterations in self-confidence and body image.

⁵¹ Fisher D, Sommerlad B. Cleft lip, cleft palate, and velopharyngeal insufficiency. *Plastic and Reconst Surg* 2011; 128(4):342e-360e

⁵² Feragen K, Kvaalem I, et al. Adolescents with and without facial difference: The role of friendships and social acceptance in perceptions of appearance and emotional resilience. *Body Image* 2010; 7:271-279

APPENDIX A
FDA Pregnancy Category Definitions

Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)	
Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

APPENDIX B

Institute of Medicine Pregnancy Weight Gain Guidelines

The Institute of Medicine (IOM) published the following new pregnancy weight gain guidelines in May 2009, to address current research that had been conducted on the effects of weight gain in pregnancy on the health of both mother and baby:⁵³

TABLE S-1 New Recommendations for Total and Rate of Weight Gain During Pregnancy, by Prepregnancy BMI

Pregpregnancy BMI	Total Weight Gain		Rates of Weight Gain* 2nd and 3rd Trimester	
	Range in kg	Range in lbs	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (< 18.5 kg/m ²)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5-24.9 kg/m ²)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0-29.9 kg/m ²)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥ 30.0 kg/m ²)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

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⁵³ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: <http://nap.edu/catalog/12584.htm>

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12/20/2011

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12/20/2011

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12/20/2011
I concur

LISA L MATHIS
12/21/2011



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

Date: October 20, 2011

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II, OND, CDER

Through: Solomon Iyasu, MD, MPH, Director
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER
Diane K Wysowski, PhD, MPH, Team Leader
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: Review of sponsor's study protocol entitled "Fetal outcomes retrospective topiramate exposure study (FORTRESS)."
Dated September 06, 2011

Drug Name(s): Qnexa (phentermine & topiramate)

Submission Number:

Application Type/Number: NDA 22580

Applicant/sponsor: Vivus

OSE RCM #: 2011-3522

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EXECUTIVE SUMMARY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), the final observational study protocol OB-901 dated September 6, 2011, a draft Summary Pooled Analysis Plan dated August 5, 2011, and the response from Vivus dated 9/16/11, in support of the New Drug Application (NDA) of Qnexa were reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

The primary objectives of the proposed study are to estimate the prevalence ratios of oral clefts (OCs) and major congenital malformations (MCMs) in newborns of women exposed to topiramate (TPM) during the first trimester of pregnancy when compared to (a) newborns of women with remote (at least 120 days prior to the index pregnancy) prior exposure to TPM or other antiepileptic drugs (AEDs); and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure. This study will be a retrospective cohort study using four databases with approximately 2,300 eligible mother-baby dyads. Each data source will produce aggregated counts of patients in contingency tables stratified by maternal age, apparent TPM indication, maternal diabetes, concomitant exposure to AEDs and other potential teratogens, and calendar time. The data coordinating center, (b) (4) will incorporate results from all databases in the study report and combine the effect estimates through a meta-analysis to compute the overall effect estimates for the prevalence ratios of OCs and MCMs among infants born to women with first trimester exposure to TPM in comparison to the comparator cohorts.

The revised study protocol and draft summary pooled analysis have incorporated some of DEPI's previous recommendations and provided more details on the study analysis plan. The estimated sample size and study power for the primary analyses (80% power to detect a relative risk of 3.4 for OCs and 90% power to detect a relative risk of 1.5 for MCMs) are acceptable based on the previously reported risk estimates for OCs (RR of 20 from the North American AED pregnancy registry data, RR of 5.2 from the pooled analysis of the Slone Epidemiology Center Birth Defects Study and the Center for Disease Control's National Birth Defects Prevention Study). However, there will be

limited sample sizes for some secondary analyses (e.g., risk estimates on dose-response relation). As a result, these analyses may not be able to provide stable estimates and the results will be difficult to interpret. Therefore, these secondary analyses should be considered as exploratory in nature.

As we have pointed out previously, it appeared in several places in the final study protocol that additional details of study methods will be provided in the Analysis and Reporting Plan which will be finalized before the study commences. The sponsor's response (3) dated 9/16/11 referred our request for this Analysis and Reporting Plan to the draft Summary Pooled Analysis Plan dated 8/5/2011. However, it is unclear whether the document was renamed or there will still be an Analysis and Reporting Plan to be submitted by the sponsor for this study.

There is also a concern about evaluating the positive predictive value (PPV) of the restrictive case definition of MCMs using a sample of approximately 300 medical records which are not necessarily from the study cohorts for the present study. We prefer that the sponsor follow our previous recommendations dated 7/19/11 to validate all potential MCM cases that will be identified in the study cohorts. Alternatively, the sponsor may restrict the validation to all of the 10 most common specific MCMs. The validation should be done in the study cohorts to enhance the validity of the study results and only validated cases should be included in the final analyses. The PPV should be estimated using both the base case definition and the secondary, more restrictive case definition. The specific recommendations to be sent to the sponsor are provided in Section 5 of this review.

1 BACKGROUND/HISTORY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), the final observational study protocol OB-901 dated September 6, 2011, a draft Summary Pooled Analysis Plan dated August 5, 2011, and the response from Vivus dated 9/16/11, in support of the New Drug Application (NDA) of Qnexa were reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

Qnexa is a combination of two marketed products, phentermine and topiramate, for which the applicant is seeking approval for the treatment of obesity and overweight. If approved, Qnexa will be available in three fixed-dose combinations of phentermine/topiramate: 3.75mg/23mg, 7.5mg/46mg, and 15mg/92mg. Recent reports based on the registry data from the U.S. and the U.K. have suggested that infants exposed to topiramate (TPM) in utero have an increased risk of oral clefts (OCs) and major congenital malformations (MCMs)^{1,2,3}.

A Complete Response letter was issued by FDA on October 28, 2010. An End of Review Conference was held on January 19, 2011, and a follow-up industry meeting was held on April 14, 2011, during which an observational study on the risk of congenital malformations, especially OCs, associated with maternal exposure to TPM during pregnancy was requested by the FDA. The results of such a study would need to be submitted to FDA in order for the sponsor to move forward with the development of Qnexa. A draft study protocol dated May 25, 2011, was reviewed by DEPI I and recommendations were sent to the sponsor. On September 21, 2011, the final study protocol (dated September 6, 2011) and a draft summary pooled analysis plan (dated August 5, 2011) were submitted to FDA for review.

The revised study protocol and summary pooled analysis plan have incorporated some of DEPI's previous recommendations following the draft protocol review. For example, the sponsor has clarified the definition of MCMs and Low birth weight (LBW); agreed to expand the case identification period for MCMs from 90 days to 365 days after birth on the infant's claim; submitted a list of tentative diagnosis and procedure codes to assemble the study cohorts and identify relevant exposures, outcomes, and covariates; provided a detailed analysis plan for the proposed propensity score approach; agreed to conduct additional sensitivity analyses to examine the robustness of the results to differing exposure and outcome definitions by repeating the main analyses for MCMs with different exposure and outcome definitions as planned for OCs; and agreed to adjust for maternal age, race, smoking, and alcohol use in the analyses for LBW.

2 REVIEW MATERIALS

The revised observational study protocol OB-901 in support of the New Drug Application (NDA) for Qnexa entitled "Fetal outcomes retrospective topiramate exposure

study (FORTRESS)” dated September 6, 2011, and the draft Summary Pooled Analysis Plan dated August 5, 2011, were reviewed. In addition, the response from Vivus dated 9/16/11 was also reviewed.

3 RESULTS OF REVIEW

3.1 STUDY OBJECTIVES

3.1.1 Proposed Study Objectives:

The *primary objectives* of the proposed study are:

- 1) to estimate the prevalence ratio of OCs in newborns of women exposed to TPM during the first trimester of pregnancy when compared to (a) newborns of women with remote (at least 120 days prior to the index pregnancy) prior exposure to TPM or other AEDs; and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure;
- 2) to estimate the prevalence ratio of MCMs in newborns of women exposed to TPM during the first trimester of pregnancy when compared to (a) newborns of women with remote prior exposure to TPM or other AEDs; and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure.

The proposed *secondary objectives* are:

- 1) to estimate the prevalence of OCs and other MCMs in newborns of women exposed to specific doses of TPM during the first trimester and to evaluate any dose response;
- 2) to estimate the prevalence of OCs and other MCMs in newborns of women exposed to TPM monotherapy compared to women exposed to AED polytherapy regimens that contain TPM;
- 3) to monitor for any signals of specific MCMs, aside from OCs, associated with TPM exposure in the first trimester;
- 4) to compare the proportion of infants with low birth weight (LBW) born to mothers exposed to TPM during pregnancy relative to infants in the

two comparator cohorts (a) newborns of women with remote prior exposure to TPM or other AEDs; and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure (this objective will be a sub study using the Kaiser Permanente database only);

- 5) to measure the background prevalence of OCs and other MCMs in all mother-infant pairs who are eligible for the study from all databases that will be used in this study;
- 6) to estimate the positive predictive value for automated claims diagnosis of OCs and MCMs using medical records as the reference standard.

3.1.2 Reviewer Comments:

The proposed study objectives are acceptable. Due to limited sample size, the proposed secondary objectives 1-3 may not be feasible to achieve. However, it is worthwhile to conduct these exploratory analyses as they may generate hypotheses on dose-response relationship and other relationships between TPM exposure and risks of OCs and MCMs.

3.2 STUDY DESIGN

3.2.1 Proposed Study Design:

This study will be a retrospective cohort study conducted in two phases. The first phase will address study objectives based on automated data only and the second phase will involve review of selected medical records for endpoint confirmation.

3.2.2 Reviewer Comments:

This reviewer agrees that a retrospective cohort study is appropriate. However, the sponsor should be aware that data from a claims-only analysis would be considered preliminary data only, unless compelling data suggesting that the outcome codes had already been validated in the same or relevant data sources are provided.

3.3 DATA SOURCES

3.3.1 Proposed Data Sources:

This study proposed to use data from the HealthCore Integrated Research Database (HIRD), OptumInsight Normative Health Information (NHI) database, Kaiser Permanente Northern and Southern California (KPNC, KPSC) Research Databases, and the Thomson Reuters MarketScan Multi-State Medicaid Research Databases.

The HealthCore HIRD database contains longitudinal health claims data on approximately 45 million individuals with medical and pharmacy benefits back to 2001. Medical records can be requested for about 75% of subjects in this database.

The OptumInsight NHI database contains medical and pharmacy claims data from 1994 with a cumulative enrollment of approximately 14 million patients. Medical records can be requested for subjects in a portion of the research database.

The KPNC and KPSC research databases contain automated clinical and pharmacy data that capture live born delivery, diagnoses of malformation, and dispensing of prescription medications. More than 3.3 million members are served by the KPNC and a similarly sized population is served by KPSC.

The Thomson Reuters MarketScan Multi-State Medicaid Research Database contains healthcare service use of individuals covered by Medicaid programs in several geographically dispersed states. The Multi-State Medicaid database dates back to 1999 and contains an average of 10 million Medicaid enrollees each year.

3.3.2 Reviewer Comments:

The use of the HealthCore HIRD database, OptumInsight NHI database, KPNC and KPSC Research Databases, and the Thomson Reuters MarketScan Multi-State Medicaid Research Databases is acceptable.

3.4 STUDY POPULATION

3.4.1 Proposed Study Population:

The study population will include women with a record of live birth during the study period and an identifiable newborn with at least 90-day post-delivery enrollment. Women eligible to enroll in this study will include those who 1) have at least 6 months of continuous enrollment in the health plan prior to the presumed conception date, and 2) are between the ages of 15 and 49 years on the delivery date.

Patients will be excluded if they have 1) a history of infection with one of the TORCH agents (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis, varicella-zoster, and parvovirus B19), 2) a history of alcohol abuse or substance abuse, or 3) an exposure to thalidomide or isotretinoin during the 6 months preceding the presumed conception date or at any point during the pregnancy.

3.4.2 Reviewer Comments:

The reviewer agrees that the study population and the inclusion/exclusion criteria are appropriate.

3.5 EXPOSURES

3.5.1 Exposures:

Mother-baby pairs exposed to TPM during the first trimester of pregnancy will be defined as those for whom prescription data indicate exposure to TPM at any dose during the first trimester. Exposure to TPM or other AEDs will be ascertained using National Drug Codes (NDCs) from prescription claims data. A woman will be considered exposed if TPM is dispensed during the exposure window (defined later in this Section) or if an earlier dispensing included enough supply to carry over into the exposure period. Exposure to TPM will be defined in two ways: 1) as an indicator variable for whether there was first trimester exposure; and 2) as a numerical variable based on calculated average daily dose.

The exposure window of the first trimester will be defined as: 1) for women who delivered at term, the earliest possible date of conception through 91 days following the latest possible date of conception, or from 287 through 168 days before delivery for singleton births or from 273 through 147 days before delivery for multiple births (note: multiple births are usually delivered earlier than single births); 2) for women with a diagnosis code of premature delivery and the length of gestation is not specified, the earliest possible date of conception through 91 days following the latest possible date of conception, or from 252 through 133 days before delivery; and 3) for those with some delivery codes indicating length of gestation, as the first 91 days of the specified gestation period.

For the first comparison cohort of mother-infant pairs with remote prior exposure to TPM or any other AEDs before the index pregnancy, eligible dispensing for prior TPM or AED exposure must have occurred at least 120 days before the date of conception to ensure that no use occurred in the index pregnancy.

Two sensitivity analyses will be conducted using two alternative definitions of the exposure window. One will be a narrower window for term deliveries which will span from 287 days to 189 days before delivery for singleton births and from 273 to 168 days before delivery for multiple births. The second one will be a more inclusive exposure definition in which the exposure window starts 30 days earlier for each scenario used in the primary case definition but does not shift the end-date for the first trimester.

3.5.2 Reviewer Comments:

This reviewer agrees that the definitions of exposure and exposure window are appropriate.

3.6 DISEASE OUTCOMES OF INTEREST

3.6.1 Proposed Study Outcomes:

Primary Outcomes:

One of the primary outcomes will be nonsyndromic OCs that are not associated with diagnosed or suspected chromosomal or genetic defects. OCs will be identified using ICD-9-CM diagnosis codes or CPT procedure codes (a preliminary list of codes was provided in the Appendix) associated with claims for physician services or hospitalization that occur within 30 days of the presumed delivery date on the mother's claims or within 365 days of birth date on the infant's claims. Mother-infant pairs who have additional claims data suggesting syndromic malformations or genetic or chromosomal defects will not qualify as cases. An alternate, more restrictive case definition that requires diagnosis of oral cleft and surgical repair with service dates up to 365 days after birth will be included in the analysis. All cases of OC will be adjudicated using medical records or longitudinal claims review as a reference standard. All confirmed OC cases will be classified as (1) cleft lip with or without cleft palate or (2) isolated cleft palate. Pooled prevalence ratios will be derived for these two outcome categories.

The other primary outcomes will be MCMs which are defined as conditions present at birth resulting from malformation, deformation, or disruption in one or more parts of the body and having serious adverse effects on the health, development, or functional ability. MCMs will be identified using ICD-9-CM diagnosis codes (a preliminary list of codes was provided in the Appendix) within 30 days of the delivery date on the mother's claims or within 365 days of birth date on the infant's claim. Mother-infant pairs who have additional claims data suggesting syndromic malformations or genetic or chromosomal defects will not qualify as cases. The sponsor proposed to evaluate the positive predictive value (PPV) of a restrictive case definition of MCMs (that requires both diagnosis and a confirmatory diagnosis of the same defects by a specialist or a condition-specific procedure code up to 365 days after birth) using a sample of approximately 300 medical records from the underlying data source.

Secondary Outcomes:

Specific MCMs other than OCs (not pre-specified) and LBW will be secondary endpoints.

3.6.2 Reviewer Comments:

The proposed alternate secondary, more restrictive case definition for MCMs (a diagnosis plus a diagnosis by a specialist or a procedure code) and OCs (a diagnosis plus surgery repair) may miss some true cases who either did not have diagnosis codes or did not have surgical or other procedures to fix the defect within 365 days after birth.

After reviewing the sponsor's response date 9/16/2011 regarding case validation (9b), we still prefer that the sponsor follow our previous recommendations dated 7/19/11 which is reiterated below. The sponsor should validate all potential MCM cases that will be identified in the study cohorts. Alternatively, the sponsor may restrict the validation to all of the 10 most common specific MCMs. The validation should be done in the study cohorts to enhance the validity of the study results and only validated cases should be included in the final analyses. The PPV should be estimated using both the base case definition and the secondary, more restrictive case definition. A sampling approach is not preferred because of the challenges of specifying appropriate sampling fraction and acceptable precision margins for PPV given the heterogeneity of malformations.

Additionally, low PPV values present a challenge in utilizing the validation data in estimating the risk.

3.7 STUDY COVARIATES

3.7.1 Proposed Study Covariates

Potential confounders in this study include maternal age, indications for TPM use, maternal diabetes, maternal obesity, exposure to known or suspected teratogens, geographic area, race, maternal alcohol use, smoking, maternal and family history of MCMs, and calendar time.

3.7.2 Reviewer Comments:

The proposed study covariates are appropriate.

3.8 SAMPLE SIZE

3.8.1 Proposed Sample Size

Based on the information from the protocol dated September 6, 2011, for the study period from 1997 (varies by data source depending on the availability of data collection) to the most recent year of available data, the expected sample size from four data sources is approximately 2,300 mother-infant dyads who had exposure to TPM during their first trimester of pregnancy.

All available mother-infant pairs who meet the exposure definition of remote (prescription dispensed at least 120 days prior to the index pregnancy) TPM or other AED will be included in the first comparison cohort.

The second comparison cohort will be selected from the universe of mother-baby dyads who did not have first trimester exposure to TPM to generate a roughly similar distribution of the apparent indications in the exposed cohort. Up to 7 unexposed mother-infant dyads for each exposed dyad will be included.

3.8.2 Reviewer Comments:

Unless the sponsor provides a justification for the currently proposal to select the second comparison cohort, the previously proposed stratified random sampling method should be used to select controls from the universe of mother-baby dyads who did not

have first trimester exposure to TPM. The sponsor should attempt to identify 7 unexposed mother-infant dyads for each exposed dyad, frequency matched by apparent indication, maternal age (<35 years or ≥ 35 years), geographic region, and calendar year of delivery.

The estimated sample size of 2,300 mother-infant dyads reflect the inclusion criteria of dyads exposed to any dose of TPM dispensed during the first trimester or 30 days preceding the presumed conception date. Those dyads have at least 6 months of eligibility before the start of pregnancy and at least 3 months of eligibility after birth. This sample size will allow 80% study power to detect a relative risk of 3.4 for OCs and 90% power to detect a relative risk of 1.5 for MCMs. However, the sample size will likely to change in the final study analyses due to the addition of recently available data and the loss caused by missing data. Nevertheless, the estimated sample size and study power for the primary analyses are acceptable based on the previously reported risk estimates for OCs (RR of 20 from the North American AED pregnancy registry data¹, RR of 5.2 from the pooled analysis of the Slone Epidemiology Center Birth Defects Study and the Center for Disease Control's National Birth Defects Prevention Study³). However, there will be limited sample sizes for some secondary analyses (e.g., risk estimates on dose-response relation). As a result, these analyses may not be able to provide stable estimates and the results will be difficult to interpret. Therefore, these secondary analyses should be considered as exploratory only. Please refer to the review from the Office of Biostatistics for further comments on sample size.

3.9 ANALYSES

3.9.1 Proposed Analyses

Descriptive statistics will be computed for demographic variables and relevant covariates and summarized within each database. Prevalence estimates of OCs and other MCMs will be computed in each database. In phase 1 of the study, results will be analyzed for OCs using the base case definition and the secondary, more restrictive case definition. In phase 2, following chart review for all potential OC cases, analyses will be conducted for cases adjudicated as “probable” or “possible”.

In the **main analyses & pooled analysis** for prevalence ratios of OCs and MCMs, several stratified analyses will be conducted within each data source. Stratification

variables will include maternal age, apparent TPM indication, maternal diabetes, and concomitant exposure to AEDs and other potential teratogens. The stratified tables will be forwarded to (b) (4) for the final pooled analysis, which will also involve stratification by site. Stratum-specific prevalence estimates and a summary prevalence ratio estimate standardized to the comparison cohort will be reported. Mantel-Haenszel-type estimators will be used as the pooled estimators for prevalence ratios. If many strata have zero margins in the stratified tables, the only results reported in the final report will be from the propensity score pooled analysis.

The second approach will involve stratification by a propensity score variable calculated within each data source. The variables that will be included to generate propensity scores include maternal age, infant sex, calendar year, geographic region, smoking, use of valproate, carbamazepine, phenytoin, other AEDs, folic acid antagonists, known or suspected teratogens, history of epilepsy, migraine, affective disorder, diabetes, hypertension, and obesity. Strata of propensity score will be defined by deciles of the propensity score distribution.

Multivariate analyses will not be performed for OCs as the number of cases will be very few. However, for the MCM outcome, a multivariate regression analysis will also be undertaken to estimate the prevalence ratio.

A number of secondary analyses are planned. Those secondary analyses will include: 1) Repeating the main analyses limiting all cohorts to women with migraine; 2) Assessing the dose-response relationship by estimating the effect of 100 mg or less per day versus more than 100 mg per day of TPM during the first trimester; 3) Assessing the duration-response relationship by evaluating whether TPM effect varies according to the number of exposed days within the first trimester; 4) Repeating the main analyses to evaluate TPM monotherapy versus multi-drug regimen including TPM. In the second phase of the study, PPV of the diagnostic and procedure codes used to identify cases of OCs will be calculated. A similar approach will be taken to calculate the PPV for the secondary, more restrictive automated case definition of MCMs.

In sensitivity analyses, the sponsor planned to examine the robustness of the results to differing exposure and outcome definitions for OCs and MCMs. The main analyses will

be repeated for OCs with differing exposure windows and using a more restrictive case definition that includes cases adjudicated as probable only and with varying length of the first trimester exposure window. Two sensitivity analyses will be conducted to evaluate the alternative definitions of the first trimester exposure window for MCMs. An additional sensitivity analysis will examine the potential effect of outcome misclassification on the prevalence ratio estimate for MCMs. Finally, an analysis will be conducted to describe the potential effect of an unmeasured confounder on study results.

An exploratory study will be conducted to assess the presence of signals for increased risks of MCMs by organ system affected. The main outcome will be the prevalence ratio of organ system-specific MCMs among women with first trimester exposure to TPM when compared to an unexposed control group. A signal will be defined as a relative risk greater than or equal to 5 when there are at least four cases across all databases.

Analyses on low birth weight will be conducted in a sub study using the Kaiser Permanente healthcare database only to provide the proportions of LBW births across cohorts and prevalence ratios. The effect of time and duration of TPM exposure will be evaluated. Analysis will adjust for covariates including maternal age, race, smoking, and alcohol use.

3.9.2 Reviewer Comment:

It appears that unadjudicated MCM cases will be included in the analyses. The sponsor should be aware that data from a claims-only analysis would be considered preliminary data, unless compelling data suggesting that the outcome codes had already been validated in the same or relevant data sources are provided. As we have recommended in the section of Disease Outcomes of Interest (3.6.2), the sponsor should validate all potential MCM cases that will be identified in the study cohorts and only validated cases should be included in the final analyses.

It will be difficult to compute the overall effect of maternal TPM exposure on infants' OCs and MCMs from the proposed stratified analyses in the main analyses that will be conducted within each data source with four stratification variables of maternal age, apparent TPM indication, maternal diabetes, and concomitant exposure to AEDs and other potential teratogens. As the outcomes of OCs are rare, many strata may not have

even one case. As stated in the draft summary pooled analysis plan, this analysis may prove problematic and the secondary propensity score stratification analysis should be used instead. The strata in the propensity score approach should be classified by quartiles instead of deciles of propensity score distribution to avoid the possible zero or low count problem associated with stratification by deciles. In addition to the primary analysis using propensity score stratification, a sensitivity analysis using propensity score matching should be performed. Another comment to the propensity score approach is that infant sex should not be included in the logistic regression model to generate propensity score as this is not a factor affecting the probability of each mother using topiramate during early pregnancy. Please refer to the review from the Office of Biostatistics (OB) for additional comments on the main analyses and pooled analysis.

Due to the limited sample size and rare outcomes, some of the proposed secondary analyses may not be able to provide stable estimates and the results will be difficult to interpret. Therefore, these secondary analyses should be considered as exploratory only.

The proposed sensitivity analyses are acceptable. An additional sensitivity analysis should be conducted using mother-infant dyads with singleton births only as children from multiple births are associated with a higher risk of birth defects, including OCs (adjusted RR=1.29, 95% CI 1.15-1.45)⁴.

The dose effect on LBW should also be evaluated in addition to the duration and time of TPM exposure in the study.

4 SUMMARY

In summary, this study protocol has incorporated many of FDA's previous recommendations and provided more details on study methods. The estimated sample size and study power for the primary analyses (80% power to detect a relative risk of 3.4 for OCs and 90% power to detect a relative risk of 1.5 for MCMs) are acceptable based on the previously reported risk estimates for OCs (RR of 20 from the North American AED pregnancy registry data¹, RR of 5.2 from the pooled analysis of the Slone Epidemiology Center Birth Defects Study and the Center for Disease Control's National Birth Defects Prevention Study³). However, there will be limited sample sizes for some secondary analyses (e.g., risk estimates on dose-response relation). As a result, these

analyses may not be able to provide stable estimates and the results will be difficult to interpret. Therefore, these secondary analyses should be considered as exploratory in nature.

As we have pointed out previously, it appeared in several places in the final study protocol that additional details of study methods will be provided in the Analysis and Reporting Plan which will be finalized before the study commences. The sponsor's response (3) dated 9/16/11 referred our request for this Analysis and Reporting Plan to the draft Summary Pooled Analysis Plan dated 8/5/2011. However, it is unclear whether the document was renamed or there will still be an Analysis and Reporting Plan to be submitted by the sponsor for this study.

There is also a concern about evaluating the PPV of the restrictive case definition of MCMs using a sample of approximately 300 medical records which will not necessarily come from the study cohorts for the present study. We prefer that the sponsor follow our previous recommendations dated 7/19/11 to validate all potential MCM cases that will be identified in the study cohorts. Alternatively, the sponsor may restrict the validation to all of the 10 most common specific MCMs. The validation should be done in the study cohorts to enhance the validity of the study results and only validated cases should be included in the final analyses. The PPV should be estimated using both the base case definition and the secondary, more restrictive case definition. Other comments on the study protocol are provided in the Results section. Recommendations to be sent to the sponsor are provided below.

5 RECOMMENDATIONS TO BE SENT TO THE SPONSOR

- *We have reviewed your response date 9/16/2011 regarding case validation (9b). We prefer that you follow our previous recommendations dated 7/19/11 to validate all potential MCM cases that will be identified in the study cohorts. Alternatively, the sponsor may restrict the validation to all of the 10 most common specific MCMs. The validation should be done in the study cohorts to enhance the validity of the study results and only validated cases should be included in the final analyses. The PPV should be estimated using both the base*

case definition and the secondary, more restrictive case definition. A sampling approach is not preferred because of the challenges of specifying appropriate sampling fraction and acceptable precision margins for PPV given the heterogeneity of malformations. Additionally, low PPV values present a challenge in utilizing the validation data in estimating the risk.

- You should justify the currently proposed mechanism to select the second comparison cohort. Otherwise, the previously proposed stratified random sampling method should be used to select controls from the universe of mother-baby dyads who did not have first trimester exposure to TPM.*
- You should attempt to identify 7 unexposed mother-infant dyads for each exposed dyad, frequency matched by apparent indication, maternal age (<35 years or ≥35 years), geographic region, and calendar year of delivery.*
- You should conduct an additional sensitivity analysis using mother-infant dyads with singleton births only.*
- The dose effect on LBW should be evaluated in addition to the duration and time of TPM exposure in the study.*
- The propensity score stratification analysis is preferred and the strata should be classified by quartiles instead of deciles of propensity score distribution. A sensitivity analysis using propensity score matching should be performed.*
- Infant sex should not be included in the logistic regression model to generate propensity scores as this is not a factor affecting the probability of a mother using TPM during early pregnancy.*
- Please clarify whether the Analysis and Reporting Plan that was cited in the study protocol was renamed as the Summary Pooled Analysis Plan or there will still be an Analysis and Reporting Plan to be submitted by the sponsor for this study.*

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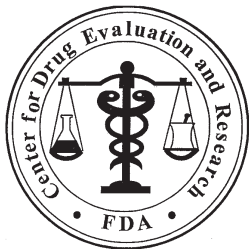
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/s/

JING JU
10/21/2011

SOLOMON IYASU
10/21/2011



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

Date: July 8, 2011

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II, OND, CDER

Through: Solomon Iyasu, MD, MPH, Director
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Judy A. Staffa, PhD, RPh, Director
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Diane K Wysowski, PhD, MPH, Team Leader
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: Review of sponsor's study protocol entitled "Fetal outcomes retrospective topiramate exposure study (FORTRESS)."

Drug Name(s): Qnexa (phentermine & topiramate)

Submission Number:

Application Type/Number: NDA 22580

Applicant/sponsor: Vivus

OSE RCM #: 2011-2077

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EXECUTIVE SUMMARY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), an observational study protocol OB-901 in support of the New Drug Application (NDA) of Qnexa entitled “Fetal outcomes retrospective topiramate exposure study (FORTRESS)” was reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

The primary objectives of the proposed study are to estimate the prevalence ratios of oral clefts (OCs) and major congenital malformations (MCMs) in newborns of women exposed to topiramate (TPM) during the first trimester of pregnancy when compared to (a) newborns of women with remote prior exposure to TPM or other antiepileptic drugs (AEDs); and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure. This study will be a retrospective cohort study using several databases (currently three data sources were proposed). Each data source will produce aggregated counts of patients in contingency tables stratified by maternal age, apparent TPM indication, maternal diabetes, concomitant exposure to AEDs and other potential teratogens, and calendar time. A data coordinating center will incorporate results from all databases in the study report and combine the effect estimates through a meta-analysis to compute the overall effect estimates for the prevalence ratios of OCs and MCMs among infants born to women with first trimester exposure to TPM in comparison to the comparator cohorts.

This protocol was incomplete as the sponsor stated in several places that additional details of study methods will be provided in the Analysis and Reporting Plan which will be finalized before the study commences. This Analysis and Reporting Plan will need to be provided for further comments. Due to the limited sample size and rare outcomes, many of the proposed analyses may not be able to provide stable estimates and the results will be difficult to interpret. There is also a concern about the validation of potential MCM cases. It seems that the sponsor will not validate the MCM cases identified from the automated data sources through medical chart review. Other comments on the study protocol are provided in the results section. Responses to sponsor’s questions and recommendations to be sent to the sponsor are provided in Section 5.

1 BACKGROUND/HISTORY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), an observational study protocol OB-901 in support of the New Drug Application (NDA) of Qnexa entitled “Fetal outcomes retrospective topiramate exposure study (FORTRESS)” was reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

Recent reports based on the registry data from the U.S. and the U.K. have suggested that infants exposed to topiramate (TPM) in utero have an increased risk of oral clefts (OCs) and major congenital malformations (MCMs). Qnexa is a combination of two marketed products, phentermine and topiramate, for which the applicant is seeking approval for the treatment of obesity and overweight. Phentermine hydrochloride was approved for the treatment of obesity on August 14, 1973. Topiramate was approved for the treatment of epilepsy on December 24, 1996 and for prophylaxis of migraine on August 11, 2004. Once approved, Qnexa will be available in three fixed-dose combinations of phentermine/topiramate: 3.75mg/23mg, 7.5mg/46mg, and 15mg/92mg.

A Complete Response letter was issued by FDA on October 28, 2010. An End of Review Conference was held on January 19, 2011 and a follow-up industry meeting was held on April 14, 2011, during which an observational study on the risk of congenital malformations, especially OCs, associated with maternal exposure to TPM during pregnancy was requested by the FDA. The results of such a study would need to be submitted to FDA in order for the sponsor to move forward with the development of Qnexa.

Per a request from the sponsor (June 17, 2011), specific questions addressed in this review include:

- Does FDA agree with the two control cohorts defined in the study protocol?
- Does FDA agree with our definition of TPM –exposed dyads for inclusion in the analysis?
- Does FDA agree with the analysis plan as outlined in the protocol?
- Does FDA agree that we could resubmit the Qnexa NDA based on the results of automated data analysis with the validation work to be submitted during the 6-month review period?

- Are there any other major issues that need to be addressed?

2 REVIEW MATERIALS

The observational study protocol OB-901 in support of the New Drug Application (NDA) for Qnexa entitled “Fetal outcomes retrospective topiramate exposure study (FORTRESS)” was reviewed.

3 RESULTS OF REVIEW

3.1 STUDY OBJECTIVES

3.1.1 Proposed Study Objectives:

The primary objectives of the proposed study are:

- 1) to estimate the prevalence ratio of OCs in newborns of women exposed to TPM during the first trimester of pregnancy when compared to (a) newborns of women with remote prior exposure to TPM or other AEDs; and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure;
- 2) to estimate the prevalence ratio of MCMs in newborns of women exposed to TPM during the first trimester of pregnancy when compared to (a) newborns of women with remote prior exposure to TPM or other AEDs; and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure.

The proposed secondary objectives are:

- 1) to estimate the prevalence of OCs and other MCMs in newborns of women exposed to specific doses of TPM during the first trimester and to evaluate any dose response;
- 2) to estimate the prevalence of OCs and other MCMs in newborns of women exposed to TPM monotherapy compared to women exposed to AED polytherapy regimens that contain TPM;
- 3) to monitor for any signals of specific MCMs, aside from OCs, associated with TPM exposure in the first trimester;

- 4) to compare the proportion of infants with low birth weight (LBW) born to mothers exposed to TPM during pregnancy relative to (a) the proportion of infants with LBW born to mothers not exposed to TPM; and to (b) the proportion of all U.S. newborns with LBW;
- 5) to measure the background prevalence of OCs and other MCMs in all mother-infant pairs who are eligible for the study from all databases that will be used in this study;
- 6) to estimate the positive predictive value for automated claims diagnosis of OCs and MCMs using medical records as the reference standard.

3.1.2 Reviewer Comments:

It is unclear from the proposed primary study objectives whether the primary outcomes of MCMs will include OCs as the FDA has suggested. The secondary objectives state that the prevalence of OCs and other MCMs will be estimated which is not consistent with the FDA's suggestion at the type B meeting on April 14, 2011. The sponsor should assess the prevalence and prevalence ratio of MCMs including OCs in the analyses for both the primary and secondary study objectives. Once the sponsor revises the "other MCMs" to "MCMs including OCs" in the study objectives, the proposed study objectives will be appropriate. However, due to limited sample size, many of these proposed objectives may not be achieved.

3.2 STUDY DESIGN

3.2.1 Proposed Study Design:

This study will be a retrospective cohort study conducted in two phases. The first phase will address study objectives based on automated data only and the second phase will involve review of selected medical records for endpoint confirmation.

3.2.2 Reviewer Comments:

This reviewer agrees that a retrospective cohort study is appropriate. However, the sponsor should be aware that data from a claims-only analysis would be considered preliminary data only, unless compelling data suggesting that the outcome codes had already been validated in the same or relevant data sources are provided.

3.3 DATA SOURCES

3.3.1 Proposed Data Sources:

This study proposed to use data from the Innovus Normative Health Information (NHI) database, Kaiser Permanente Northern and Southern California (KPNC, KPSC) Research Databases, and the Thomson Reuters MarketScan Multi-State Medicaid Research Databases.

The Innovus NHI database contains medical and pharmacy claims data from 1994 with a cumulative enrollment of approximately 14 million patients. Medical records can be requested for subjects in a portion of the research database.

The KPNC and KPSC research databases contain automated clinical and pharmacy data that capture delivery, diagnoses of malformation, and dispensing of prescription medications.

The Thomson Reuters MarketScan Multi-State Medicaid Research Database contains healthcare service use of individuals covered by Medicaid programs in several geographically dispersed states. The Multi-State Medicaid database dates back to 1999 and contains an average of 10 million Medicaid enrollees each year.

3.3.2 Reviewer Comments:

The use of the Innovus NHI database, KPNC and KPSC Research Databases, and the Thomson Reuters MarketScan Multi-State Medicaid Research Databases is acceptable. However, due to the concern of limited sample size, the sponsor should keep exploring the feasibility of using other healthcare databases that contain large numbers of mother-baby dyads. With the withdrawal of the HealthCore Integrated Research Database from the originally proposed data sources, it may become possible to use the databases that contain overlapping data with HealthCore. The sponsor should also provide the States that are included in the Thomson Reuters MarketScan Multi-State Medicaid Research Databases and explore the possibility of including additional Medicaid data in the study.

3.4 STUDY POPULATION

3.4.1 Proposed Study Population:

The study population will include women with a record of live birth during the study period and an identifiable newborn with at least 90-day post-delivery enrollment. Women eligible to enroll in this study will include those who 1) have at least 6 months of continuous enrollment in the health plan prior to the presumed conception date, and 2) are between the ages of 15 and 49 years on the delivery date.

Patients will be excluded if they have 1) a history of infection with one of the TORCH agents (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis, varicella-zoster, and parvovirus B19), 2) a history of alcohol abuse or substance abuse, or 3) an exposure to thalidomide or isotretinoin during the 6 months preceding the presumed conception date or at any point during the pregnancy.

3.4.2 Reviewer Comments:

The reviewer agrees that the study population and the inclusion/exclusion criteria are appropriate. However, the protocol should describe and justify a method on how history of infection with TORCH agents and history of alcohol abuse or substance abuse will be identified and confirmed using claims data.

3.5 EXPOSURES

3.5.1 Exposures:

Mother-baby pairs exposed to TPM during the first trimester of pregnancy will be defined as those for whom prescription data indicate exposure to TPM at any dose during the first trimester. A woman will be considered exposed if TPM is dispensed during the exposure window (defined later in Section 3.5.1) or if an earlier dispensing included enough supply to carry over into the exposure period. Exposure to TPM will be defined in two ways: 1) as an indicator variable for whether there was first trimester exposure; and 2) as a numerical variable based on calculated average daily dose.

For the first comparison cohort of mother-infant pairs with prior exposure to TPM or any other AEDs before the index pregnancy, eligible dispensing for prior TPM or

AED exposure must have occurred at least 120 days before the date of conception to ensure that no use occurred in the index pregnancy.

Exposure to TPM or other AEDs will be ascertained using NDCs from prescription claims data.

The exposure window of the first trimester will be defined as: 1) for women who delivered at term, the earliest possible date of conception through 91 days following the latest possible date of conception, or from 287 through 168 days before delivery for singleton births or from 273 through 147 days before delivery for multiple births; 2) for women with a diagnosis code of premature delivery and the length of gestation is not specified, the earliest possible date of conception through 91 days following the latest possible date of conception, or from 252 through 133 days before delivery; and 3) for those with some delivery codes indicating length of gestation, as the first 91 days of the specified gestation period.

Two sensitivity analyses will be conducted using two alternative definitions of the exposure window. One will be a narrower window for term deliveries which will span from 266 days to 176 days before delivery. The second one will be a more inclusive exposure definition in which the exposure window starts 30 days earlier for each scenario used in the primary case definition but does not shift the end-date for the first trimester.

3.5.2 Reviewer Comments:

This reviewer agrees that the definitions of exposure and exposure window are appropriate.

3.6 DISEASE OUTCOMES OF INTEREST

3.6.1 Proposed Study Outcomes:

Primary Outcomes:

One of the primary outcomes will be nonsyndromic OCs that are not associated with diagnosed or suspected chromosomal or genetic defects. OCs will be identified using ICD-9-CM diagnosis codes or CPT procedure codes (a preliminary list of codes was provided in the Appendix) associated with claims for physician services or hospitalization that occur within 30 days of the presumed delivery date on the mother's claims or within 365 days of birth date on the infant's claims. Mother-infant pairs who

have additional claims data suggesting syndromic malformations or genetic or chromosomal defects will not qualify as cases. All cases of OC will be adjudicated using medical records or longitudinal claims review as a reference standard.

The other primary outcomes will be MCMs which are defined as conditions present at birth resulting from malformation, deformation, or disruption in one or more parts of the body and having serious adverse effects on the health, development, or functional ability. MCMs will be identified using ICD-9-CM diagnosis codes (a preliminary list of codes was provided in the Appendix) within 30 days of the delivery date on the mother's claims or within 90 days of birth date on the infant's claim. Mother-infant pairs who have additional claims data suggesting syndromic malformations or genetic or chromosomal defects will not qualify as cases. The sponsor proposed to evaluate the positive predict value (PPV) of a restrictive case definition of MCMs (requires both diagnosis and procedure codes up to 365 days after birth) using a sample of approximately 200 medical records from the underlying data source.

Secondary Outcomes:

Specific MCMs other than OCs (not pre-specified) and LBW will be secondary endpoints.

3.6.2 Reviewer Comments:

The sponsor should clarify whether the primary outcomes of MCMs will include OCs or not. The proposed alternate secondary, more restrictive case definition that requires both diagnosis and procedure codes for MCMs and OCs may miss some true cases who either did not have diagnosis codes or did not have surgical or other procedures to fix the defect within 365 days after birth. The sponsor should identify the cases of MCMs within 30 days of the delivery date on the mother's claims or within 365 days (instead of 90 days) of birth date on the infant's claim.

It is unclear the purpose of the sponsor's proposal to evaluate the positive predict value (PPV) of a restrictive case definition of MCMs (requires both diagnosis and procedure codes up to 365 days after birth) using a sample of approximately 200 medical records from the underlying data source, especially when those potential cases are not

necessarily restricted to the study cohorts in the study. The sponsor did not provide information on how the estimated PPV will be utilized in the study. Ideally, the sponsor should validate all potential cases of MCMs identified from the automated data. If the sponsor chooses to validate a subset of potential cases, the sponsor should provide a justification for not validating all cases. The subset of cases to be validated should be chosen scientifically (describe and justify selection method) from the potential cases identified in the study cohorts. The sponsor should estimate the PPV using both the base case definition and the secondary, more restrictive case definition.

The sponsor should have provided the definition of study outcome of LBW in the proposal.

3.7 STUDY COVARIATES

3.7.1 Proposed Study Covariates

Potential confounders in this study include maternal age, indications for TPM use, maternal diabetes, maternal obesity, exposure to known or suspected teratogens, geographic area, race, maternal alcohol use, smoking, maternal and family history of MCMs, and calendar time.

3.7.2 Reviewer Comments:

The proposed study covariates are appropriate. However, the sponsor should finalize the list of diagnosis and procedure codes to assemble the study cohorts and identify relevant exposures, outcomes, and covariates and submit to the FDA for further evaluation.

3.8 SAMPLE SIZE

3.8.1 Proposed Sample Size

Based on the most current information from the sponsor (submitted on June 17, 2011), for the study period from 1997 (varies by data source depending on the availability of data collection) to the most recent year of available data, the expected sample size from three data sources is approximately 1400 mother-infant dyads (697 from Innovus NHI data, 218 from Kaiser Northern and Southern California, and 500

from Thomson Reuters MarketScan Multi-State Medicaid data) who had exposure to TPM during their first trimester of pregnancy.

All available mother-infant pairs who meet the exposure definition of remote (prescription dispensed at least 120 days prior to the index pregnancy) TPM or other AED will be included in the first comparison cohort.

The second comparison cohort will be selected by stratified random sampling method from the universe of mother-baby dyads who did not have first trimester exposure to TPM. The sponsor will attempt to identify 7 unexposed mother-infant dyads for each exposed dyad, frequency matched by apparent indication, maternal age (<35 years or ≥35 years), geographic region, and calendar year of delivery.

3.8.2 Reviewer Comments:

The estimated sample size of 1400 mother-infant dyads reflect the inclusion criteria of dyads exposed to any dose of TPM dispensed during the first trimester or 30 days preceding the presumed conception date. Those dyads have at least 6 months of eligibility before the start of pregnancy and at least 3 months of eligibility after birth. However, the sample size will be reduced after applying the exclusion criteria. Please refer to the review from the Office of Biostatistics for further comments on sample size.

3.9 ANALYSES

3.9.1 Proposed Analyses

Descriptive statistics will be computed for demographic variables and relevant covariates and summarized within each database. Prevalence estimates of OCs and other MCMs will be computed in each database. In phase 1 of the study, results will be analyzed for OCs using the primary case definition and the secondary, more restrictive case definition. In phase 2, following chart review for all potential OC cases, analyses will be conducted for cases adjudicated as “probable” or “possible”. In contrast, all MCM cases identified in the automated data will be included in the analysis.

In the main analyses for prevalence ratios of OCs and MCMs, several stratified analyses will be conducted within each data source. Stratification variables will include maternal age, apparent TPM indication, maternal diabetes, and concomitant exposure to

AEDs and other potential teratogens. Stratum-specific prevalence estimates and a summary prevalence ratio estimate standardized to the comparison cohort will be reported. In addition to stratified analyses, propensity score adjusted analyses will be conducted within each data source. Additional details of the propensity score adjustment will be provided in the Analysis and Reporting Plan. Multivariate analyses will be precluded for OCs as the number of cases will be very few. However, for the MCM outcome, a multivariate regression analysis will also be undertaken to estimate the prevalence ratio.

A number of secondary analyses are planned. Unless otherwise indicated, all will be completed with automated data only. Those secondary analyses will include 1) Repeating the main analyses limiting all cohorts to women with migraine; 2) Assessing the dose-response relationship by estimating the effect of 100 mg or less per day versus more than 100 mg per day of TPM during the first trimester; 3) Assessing the duration-response relationship by evaluating whether TPM effect varies according to the number of exposed days within the first trimester; 4) Repeating the main analyses to evaluate TPM monotherapy versus multi-drug regimen including TPM. In the second phase of the study, PPV of the diagnostic and procedure codes used to identify cases of OCs will be calculated. A similar approach will be taken to calculate the PPV for the secondary, more restrictive automated case definition of MCMs.

In sensitivity analyses, the sponsor planned to examine the robustness of the results to differing exposure and outcome definitions. The main analyses will be repeated for OCs using a more restrictive case definition that includes cases adjudicated as probable only and with varying length of the first trimester exposure window. An additional sensitivity analysis will examine the potential effect of outcome misclassification on the prevalence ratio estimate for MCMs. Finally, an analysis will be conducted to describe the potential effect of an unmeasured confounder on study results.

An exploratory study will be conducted to assess the presence of signals for increased risks of MCMs by organ system affected. The main outcome will be the prevalence ratio of organ system-specific MCMs among women with first trimester exposure to TPM

when compared to an unexpected control group. A signal will be defined as a relative risk greater than or equal to 5 when there are at least four cases across all databases.

Analyses on low birth weight will be conducted to provide the proportions of LBW births across cohorts and prevalence ratios. The effect of time, dose, and duration of TPM exposure will be evaluated. An analysis focused on any exposure in the third trimester will be conducted. The proportion of LBW infants in the exposed cohort will be compared to the national standard.

3.9.2 Reviewer Comment:

It appears that unadjudicated MCM cases will be included in the analyses. The sponsor should be aware that data from a claims-only analysis would be considered preliminary data only, unless compelling data suggesting that the outcome codes had already been validated in the same or relevant data sources are provided.

It will be difficult to compute the over effect of maternal TPM exposure on infants' OCs and MCMs from the proposed stratified analyses in the main analyses that will be conducted within each data source with four stratification variables of maternal age, apparent TPM indication, maternal diabetes, and concomitant exposure to AEDs and other potential teratogens. As the outcomes of OCs are rare, many strata may not have even one case. The sponsor also proposed that propensity score adjusted analyses will be conducted within each data source but did not provide detailed information. The sponsor should provide a detailed analysis plan for the proposed propensity score approach. Please refer to the review from the Office of Biostatistics for further comments on the main analyses.

Due to the limited sample size and rare outcomes, many of the proposed secondary analyses may not be able to provide stable estimates and the results will be difficult to interpret.

For sensitivity analyses, it is unclear whether the sponsor will repeat the main analyses for MCMs with different exposure and outcome definitions as they planned for OCs. The sponsor should provide more details on the two sensitivity analyses examining

the potential effect of outcome misclassification on the prevalence ratio estimate for MCMs and the potential effect of an unmeasured confounder on study results.

A signal was defined as a relative risk greater than or equal to 5 in the exploratory study to assess the presence of signals for increased risk of MCMs by organ system affected. The sponsor should provide justification for the choice of a relative risk of 5 or greater for the signal definition.

For the LBW study, additional analysis should be planned to fulfill the proposed study objective-- “to compare the proportion of infants born to mothers exposed to TPM who are born with low birth weight (LBW) relative to the proportion of infants with LBW born to mothers not exposed to TPM”. The analyses would need to include adjustment for maternal age, race, smoking, and alcohol use.

3.10 DATA MANAGEMENT & METHOD TO COMBINE RESULTS FROM DATA SOURCES

3.10.1 Proposed Data Management

The proposed exposure and outcome definitions and analysis strategy will be applied to all data sources. Each data source will produce aggregated counts of patients in contingency tables stratified by apparent indication, patient age, calendar time, and other covariates of interest. A data coordinating center will incorporate results from all databases in the study report and combine the effect estimates through a meta-analysis to compute an overall effect estimates for the prevalence ratios of OCs and MCMs among infants born to women with first trimester exposure to TPM in comparison to the comparator cohorts.

Two different approaches will be specified in the meta-analysis plan to be finalized prior to data delivery by all data sources. The first will use stratified analysis with data source as a stratification variable. Each data provider will supply highly stratified contingency tables with counts of patients by exposure and outcome status. Summary prevalence ratio estimates will be combined across strata using standardization. The second approach to combining results across data sources will involve inverse variance weighting of the adjusted PR estimates which will be obtained through propensity score or multivariable regression methods from each data source. The details of each analysis

will be described in an Analytic and Reporting Plan which will be finalized before the study commences.

3.10.2 Reviewer Comments:

As the number of OC cases is expected to be few, many cells in the stratified contingency tables may be zero from each data source. The sponsor should provide the details on the methods to compute the overall effect for the prevalence ratios of OCs and MCMs from different data sources in the finalized Analytic and Reporting Plan. Please refer to the review from the Office of Biostatistics for more comments on the proposed data management and method to combine results from data sources.

4 SUMMARY

In summary, this study protocol provided some insight on how this study will be conducted. However, this protocol was incomplete as the sponsor stated in several places that additional details of study methods will be provided in the Analysis and Reporting Plan which will be finalized before the study commences. This Analysis and Reporting Plan will need to be provided for further comments. Additionally, the limited sample size to achieve the proposed study objectives, especially the secondary objectives (e.g., risk estimates on dose-response relation), remains a concern. Due to the limited sample size and rare outcomes, many of the proposed analyses may not be able to provide stable estimates and the results will be difficult to interpret. There is also a concern about the validation of potential MCM cases. It seems that the sponsor will not validate the MCM cases identified from the automated data sources through medical chart review. The sponsor should be aware that data from a claims-only analysis would be considered preliminary data only. Other comments on the study protocol are provided in the results section. Responses to sponsor's questions and recommendations to be sent to the sponsor are provided below.

5 RECOMMENDATIONS TO BE SENT TO THE SPONSOR

In response to the sponsor's request, comments on the following questions are provided.

- Does FDA agree with the two control cohorts defined in the study protocol?

Yes.

- Does FDA agree with our definition of TPM –exposed dyads for inclusion in the analysis?

Yes.

- Does FDA agree with the analysis plan as outlined in the protocol?

More details on the analytical methods for each analysis and the approaches to combine results across data sources should be provided to FDA. Please review the comments from FDA's Statisticians and submit the finalized Analytic and Reporting Plan for further comments.

- Does FDA agree that we could resubmit the Qnexa NDA based on the results of automated data analysis with the validation work to be submitted during the 6-month review period?

Please refer to the DMEP, OND for final decision and additional comments on conditions for resubmission of Qnexa NDA. In terms of this proposed observational study alone, you should be aware that data from a claims-only analysis would be considered preliminary data only, unless compelling data suggesting that the outcome codes had already been validated in the same or relevant data sources are provided. A complete and final study protocol should be submitted to the FDA for review to determine if it is acceptable for initiating the study.

- Are there any other major issues that need to be addressed?

Yes. Please see the following recommendations:

- *You should keep exploring the feasibility of using other healthcare databases that contain large numbers of mother-baby dyads. With the withdrawal of the HealthCore Integrated Research Database from the originally proposed data sources, it may become possible to use other databases that contain overlapping data with HealthCore.*
- *You should provide the list of States that are included in the Thomson Reuters MarketScan Multi-State Medicaid Research Databases and explore the possibility to include additional Medicaid data in the study.*

- *You should describe and justify a method on how history of infection with TORCH agents and history of alcohol abuse or substance abuse will be identified and confirmed using claims data.*
- *You should assess the prevalence and prevalence ratio of MCMs including OCs in analyses for both the primary and secondary study objectives.*
- *You should identify the cases of MCMs within 30 days of the delivery date on the mother's claims or within 365 days, instead of 90 days, of birth date on the infant's claim.*
- *Ideally, you should validate all potential cases of MCMs identified from the automated data. If you choose to validate a subset of potential cases, you should justify your choice. The subset of cases to be validated should be chosen scientifically from the potential cases identified in the study cohorts and the PPV should be estimated using both the base case definition and the secondary, more restrictive case definition.*
- *You should provide the definition of the secondary study outcome of LBW.*
- *You should finalize the list of diagnosis and procedure codes to assemble the study cohorts and identify relevant exposures, outcomes, and covariates and submit to the FDA for further evaluation.*
- *You should provide a detailed analysis plan for the proposed propensity score approach.*
- *You should conduct sensitivity analyses to examine the robustness of the results to differing exposure and outcome definitions by repeating the main analyses for MCMs with different exposure and outcome definitions as you planned for OCs.*
- *You should provide more details on the two sensitivity analyses examining the potential effect of outcome misclassification on the prevalence ratio estimate for MCMs and the potential effect of an unmeasured confounder on study results.*

- *You should provide justification for the signal definition of a relative risk greater than or equal to 5 in the exploratory study to assess the presence of signals for increased risk of MCMs.*
- *You should conduct additional analysis to compare the proportion of infants with LBW born to mothers exposed to TPM relative to the proportion of infants with LBW born to mothers not exposed to TPM.*
- *The analyses on LBW should be adjusted for maternal age, race, smoking, and alcohol use.*
- *You should plan appropriate analyses to fulfill the study objective--“to measure the background prevalence of OCs and MCMs in all mother-infant pairs who are eligible for the study from all databases that will be used in this study”.*
- *You should provide a finalized meta-analysis plan and details on the methods to compute the overall effect for the prevalence ratios of OCs and MCMs from different data sources for further evaluation.*

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/s/

JING JU
07/15/2011

SOLOMON IYASU
07/15/2011

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

REVIEW DEFERRAL MEMO

Date: November 1, 2010

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

From: Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer
Division of Risk Management

Subject: Review Deferred: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): QNEXA (phentermine/topiramate) Extended Release Capsule

Application Type/Number: NDA 22-580

Applicant/Sponsor: Vivus, Inc.

OSE RCM #: 2010-130

This memorandum documents the deferral of our review of QNEXA (phentermine/topiramate) Extended Release Capsule. On January 14, 2010, the Division of Metabolism and Endocrinology Products (DMEP) requested that DRISK review the sponsor's proposed Medication Guide (MG).

On October 28, the Division of Metabolism and Endocrinology issued a Complete Response (CR) due to clinical deficiencies. DMEP does not plan to address labeling at this time. Therefore, DRISK defers comment on the sponsor's MG at this time. A final review will be performed after the sponsor submits patient labeling to the Complete Response letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

BARBARA A FULLER

11/01/2010

DRISK Consult Defer memo for Qnexa (phentermine/topiramate)

LASHAWN M GRIFFITHS

11/01/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)
To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22580 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Qnexa Established/Proper Name: phentermine + topiramate Dosage Form: capsule Strengths: 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, 15 mg/92 mg		
Applicant: Vivus, Inc. Agent for Applicant (if applicable):		
Date of Application: 12/28/09 Date of Receipt: 12/28/09 Date clock started after UN: N/A		
PDUFA Goal Date: October 28, 2010		Action Goal Date (if different):
Filing Date: February 26, 2010		Date of Filing Meeting: February 22, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s): 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 ³ 30 kg/m ²), or overweight patients (BMI ³ 27 kg/m ²) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR	

<input type="checkbox"/> Direct-to-OTC		314.510/21 CFR 601.41)		
Other:		<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 068651				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified: N/A			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee</i>	Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			

<i>staff.</i>	
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small.</i>	

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment															
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X																	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X																	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?			X																	
<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p> <p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>20505</td> <td>Topamax</td> <td>PED(method of use patent)</td> <td>6/22/2013</td> </tr> <tr> <td>20505</td> <td>Topamax</td> <td>M54(method of use patent)</td> <td>12/22/2012</td> </tr> <tr> <td>20844</td> <td>Topamax</td> <td>PED M-54</td> <td>6/22/2013 12/22/2012</td> </tr> </tbody> </table>		Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	20505	Topamax	PED(method of use patent)	6/22/2013	20505	Topamax	M54(method of use patent)	12/22/2012	20844	Topamax	PED M-54	6/22/2013 12/22/2012	X Qnexa is for a new indication		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
20505	Topamax	PED(method of use patent)	6/22/2013																	
20505	Topamax	M54(method of use patent)	12/22/2012																	
20844	Topamax	PED M-54	6/22/2013 12/22/2012																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
Exclusivity		YES	NO	NA	Comment															
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X																	
<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				X																
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements)		X																		

<i>only)</i> If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
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Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?	X			

If yes, date consult sent to the Controlled Substance Staff: 12/30/09				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i></p> <p><i>Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>		X		requested
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	X			
<i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (b) (4)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	X			
<i>If no, request in 74-day letter.</i>				
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?			X	
<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			
<i>If yes, specify consult(s) and date(s) sent:</i>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): May 2, 2007	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 22, 2009	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): April 18, 2007, August 15, 2007, August 29, 2007	X			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 22, 2010

BLA/NDA/Supp #: 022580

PROPRIETARY NAME: Qnexa

ESTABLISHED/PROPER NAME: immediate-release phentermine hydrochloride beads and modified-release topiramate beads formulated for oral administration.

DOSAGE FORM/STRENGTH: Capsules: 3.75mg/23 mg, 7.5mg/46 mg, 11.25mg/69 mg, 15mg/92 mg

APPLICANT: Vivus, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): 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 \geq 30 kg/m²), or overweight patients (BMI \geq 27 kg/m²) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pooja Dhaira (initially – Pat Madara)	Y
	CPMS/TL:	Lina Aljuburi	Y
Cross-Discipline Team Leader (CDTL)	Eric Colman		Y
Clinical	Reviewer:	Mary Roberts	Y
	TL:	Eric Colman	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Johnny Lau	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Lee Ping Pian	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Carlson	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	TBD	N
	TL:	TBD	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Joseph Leginus	N
	TL:	Su Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	TBD	
	TL:	TBD	
OSE/DMEPA (proprietary name)	Reviewer:	Ann Crandall	N
	TL:	Melina Griffis	Y
OSE/DRISK (REMS)	Reviewer:	LaShawn Griffiths	Y
	TL:	Mary Dempsey	Y
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	N
	TL:	Tejashri Purohit-Sheth	N

Other reviewers	Chad Reissig, CSS Lori Love, CSS TL Ginneh Stowe, Peds June Cai, SEALD Endpoints	Y Y Y Y
Other attendees		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,</i> 	<input checked="" type="checkbox"/> YES Date if known: July 15, 2010 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<i>mitigation, treatment or prevention of a disease</i>	
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<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments: N/A</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Eric Colman, M.D.; Deputy Director of DMEP 21st Century Review Milestones (see attached) (optional): Comments: 21 st Century Review procedures will be followed	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
X	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
N/A	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
N/A	BLA/BLA supplements: If filed, send 60-day filing letter
N/A	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
X sent	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it

does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
08/17/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 9, 2010

TO: Mary H. Parks, M.D.
Director, Division of Metabolism and Endocrinology
Products

FROM: Xikui Chen, Ph.D.
Chemist
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 7/9/2010*
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-580, Qnexa®
(phentermine/topiramate) Capsule (VI-0521), Sponsored
by Vivus Inc.

At the request of the Division of Metabolism and Endocrinology Products, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study# OB-109: "A randomized, open-label, six-treatment, parallel, single dose study to assess bioequivalence of the two oral capsule formulations of the combination product VI-0521 in healthy obese subjects"

The clinical portion of this study was conducted at Celerion (formerly known as MDS Pharma Services), Tempe, AZ. Following the inspection of Celerion in Arizona (6/28-7/7/2010), no Form FDA-483 was issued. The analytical portion was conducted at

(b)(4) Form FDA-483 was issued. Response from (b)(4) to the Form 483 has not been received as of the date of this writing. We will amend this memorandum if the response from (b)(4) changes our conclusion. Our evaluation of the inspectional findings follows:

1. Although the run acceptance criteria for calibration standards and quality control samples were met, two analytical runs # 2 and 31 for Phentermine were re-assayed and rejected due to improbable contaminations.

(b)(4) re-assayed samples in analytical runs # 2 and 31 for Phentermine in runs # 40 and 44, respectively, although the run acceptance criteria for calibration standards, quality control samples and blank controls were all met. (b)(4) explanation was that the samples in runs #2 and #31 might be contaminated. However, based on remarks recorded in the Sample Preparation Form audited during the inspection, DSI found that sample contaminations in these two runs can not be substantiated.

(b)(4) rejected the data from runs # 2 and 31, and reported the data from runs 40 and 44 in the analytical report. DSI is of the opinion that there is no failed-run evidence to reject runs # 2 and 31, and the phentermine data generated from these two runs should be accepted, reported and utilized in the bioequivalence determination.

2. 170 study samples identified Unacceptable Internal Standard Response (UISR) for Topiramate were re-assayed and the data for these UISR samples were rejected.

(b)(4) re-assayed a large number (n=170) of topiramate study samples listed in Table 6 " Summary of re-assay of analytical reasons" of the analytical report because these samples were identified as having Unacceptable Internal Standard Response (UISR). Subsequently, (b)(4) rejected the original data and reported the re-assayed data in the study report submitted to the Agency. As majority (98%) of the re-assayed data and the original data are similar (<20%), the original data should have been reported. Moreover, DSI found that the run acceptance criteria for calibration standards, quality control samples and blank controls were all met for the runs in which these UISR samples were analyzed.

DSI is of the opinion that the original data of the 170 UISR samples should be used in the bioequivalence evaluation for Topiramate.

3. Failure to follow your SOP, Laboratory Documentation, SOP number 03.01.009 version 19, dated 30-Apr-2009.

Specifically, (b)(4) Maintenance Logs, LH5 S/N 550450N4507, LH2, S/N 550235N4655, in review of these logs the "Disclosed

To And Understood By" section should be signed and dated within 2 business days of signature date. The disclosed signature was not signed until 8 months later, and the "Verified By Date" was signed after the Disclosed Signature. In review of LC/MS# 19 S/N 5061020B, the "disclosed To And Understood By" section is again signed late. Some pages are marked "late Review" Some are not.

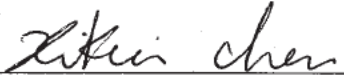
(b) (4) should implement steps to assure that their operation procedures for laboratory documentation are followed in their future studies.

Conclusion:

Following our evaluation of the inspectional findings, the Division of Scientific Investigations recommends the following:

1. Data from analytical runs # 2 and 31 for Phentermine should be accepted and utilized in the bioequivalence evaluation (see discussion in 483 Item 1).
2. Data of the 170 UISR samples prior to re-assay, coded as UISR in Table 6 "summary of reassay for analytical reasons" of the bioanalytical report, should be accepted and utilized in the bioequivalence evaluation for Topiramate (see discussion in 483 Item 2).

After you have reviewed this transmittal memo, please append it to the original NDA submission.


Xikui Chen, Ph.D.

Final Classification:

(b)(4)

NAI - Celerion, Tempe, AZ

cc: DARRTS
DSI/Ball/Haidar
DSI/Yau/Rivera-Lopez/CF
OND/DMEP/Pooja Dharja/Mary Parks
OTS/OCF/Johnny Lau/Sally Choe
HFR-PA2535/Allen Hall (BIMO)
HFR-SW350/Carl Montgomery (BIMO)

HFR-PA2540/Armando Chavez
HFR-SW3515/Ismael Olvera

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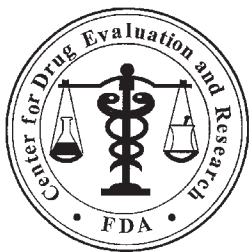
cc: email
CDER DSI PM TRACK

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

XIKUI CHEN
07/09/2010



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

Date: June 18, 2010

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II, OND, CDER

Through: Tarek A. Hammad, MD, PhD, MSc, MS, Associate Director
Division of Epidemiology
Office of Surveillance and Epidemiology, CDER

Diane K Wysowski, PhD, MPH, Acting Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology, CDER

From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
Division of Epidemiology
Office of Surveillance and Epidemiology, CDER

Subject: Literature review for associations of congenital anomalies
with phentermine and topiramate separately and co-
administered

Drug Name(s): Qnexa (phentermine & topiramate)

Application Type/Number: NDA 22580

Submission Number:

Applicant/sponsor: Vivus Inc.

OSE RCM #: 2010-500

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EXECUTIVE SUMMARY

The Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology in the Office of Surveillance and Epidemiology (OSE) to review the literature for associations of congenital anomalies with phentermine and topiramate used separately and co-administered.

A literature search was conducted in PubMed until April 23, 2010. A total of four cohort studies, one on phentermine use and three on topiramate use, and three case reports on adverse pregnancy outcomes of topiramate, were identified in this review. No relevant study on the concomitant use of phentermine and topiramate was identified in current literature.

The congenital malformations associated with phentermine and topiramate use were varied in the studies and case reports identified in the literature review. Due to a limited number of studies and the small sample size in each study, a pattern of congenital malformations could not be determined. However, unfavorable pregnancy outcomes were generally more frequent in the exposed groups, although most outcomes were not statistically significantly different from the controls. The magnitude and absolute risk of congenital anomalies associated with topiramate and phentermine use alone or in combination is not known because each study identified in this review had significant limitations and many of the analyses were not adjusted for confounders.

Adverse pregnancy outcomes associated with phentermine and fenfluramine use reported in a cohort study included cardiomyopathy, muscular ventricular septal defect, small left colon syndrome, and bilateral indirect inguinal hernias⁹. Adverse pregnancy outcomes associated with topiramate use alone reported in published cohort studies and case reports included increased frequencies of spontaneous abortions, induced abortions, ectopic pregnancies, low birth weight, major congenital malformations of pulmonary artery stenosis, multiple brain cysts with neonatal seizures, neonatal hypocalcemic seizures, cleft lip and palate, hypospadias, and agenesis of the thumb and phalanges, and minor congenital malformations of sacral dimple, clicky hips, plagiocephaly, toe webbing, and immature hip joints. There are no data on adverse pregnancy outcomes associated with concomitant use of phentermine and topiramate.

With the use of topiramate and phentermine in obese women, the number of pregnancies with exposure to these two agents is expected to be much higher than currently. To avoid the potential drug-associated risk of congenital anomalies and to follow the general recommendation of not attempting to lose weight while pregnant, we do not recommend the use of phentermine and topiramate in combination for the treatment of obesity in pregnant women. More studies are needed on the association between congenital malformations and phentermine and topiramate when used separately or concomitantly in women during pregnancy.

1 INTRODUCTION

The Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology in the Office of Surveillance and Epidemiology (OSE) to review the literature for associations of congenital anomalies with phentermine and topiramate separately and co-administered. An advisory committee meeting is scheduled to discuss the safe use of Qnexa (phentermine & topiramate) for the treatment of obesity on July 15, 2010.

Phentermine hydrochloride was approved for the treatment of obesity on August 14, 1973 under the brand name of Fastin that was later discontinued. Currently, generic phentermine products are available in the U.S. Topiramate was approved for the treatment of epilepsy on December 24, 1996 and for prophylaxis of migraine on August 11, 2004.

Some studies have found an increased risk of congenital anomalies in women who are obese compared with women of normal weight^{1,2,3}. However, one study⁴ concluded that maternal weight alone was not associated with an increase in congenital anomalies. Instead, diabetes was significantly associated with the increase in the rate of anomalies. The identification of maternal weight as a risk factor in epidemiologic studies may be a surrogate for pregestational diabetes. Nevertheless, it is recommended that women should optimize their weight before pregnancy and no weight loss should be attempted during pregnancy.

It is widely accepted that prenatal exposure to antiepileptic drugs (AEDs), but not the epilepsy itself, increases the risk of congenital anomalies of offspring^{5,6,7,8}. However, there are limited data on teratogenic effects of topiramate, a newer agent in the class of AEDs. Similarly, there are limited data on adverse pregnancy outcomes of phentermine use. This literature review was conducted to determine if phentermine, topiramate, and the drugs combined increase the risk of congenital anomalies in exposed women.

2 METHODS & MATERIALS REVIEWED

A literature search was conducted in PubMed until April 23, 2010. The keywords used in the search were listed below.

- "phentermine" AND ("congenital abnormalities" OR ("congenital" AND "abnormalities") OR ("congenital" AND "anomalies") OR "congenital anomalies" OR "pregnancy outcome")
- "topiramate" AND ("congenital abnormalities" OR ("congenital" AND "abnormalities") OR ("congenital" AND "anomalies") OR "congenital anomalies" OR "pregnancy outcome")
- "phentermine" AND "topiramate"

A total of four cohort studies on adverse pregnancy outcomes, one with phentermine use and three with topiramate use, were identified from these PubMed searches. Additionally, three case reports on adverse pregnancy outcomes with topiramate use were identified. No relevant study on the concomitant use of phentermine and topiramate was identified in this review.

3 RESULTS & OSE COMMENTS

3.1 PHENTERMINE

This review identified only one study on pregnancy outcomes with phentermine use. A brief summary and critique of the study are provided below.

3.1.1 Study Synopsis

A controlled prospective cohort study conducted by Jones et al.⁹ compared the pregnancy outcomes in 98 women who had taken phentermine and fenfluramine to 233 women who had not. From June 1996 through January 1998, 191 pregnant women made calls to the California Teratogen Information Service and Clinical Research Program requesting information on the potential teratogenic effects of phentermine and fenfluramine and reported having taken these drugs for any length of time during their current pregnancies. Among them, 98 women who were accessible by telephone and agreed to the study protocol for evaluation of outcome were enrolled in the exposed cohort. Pregnant women who called during the same time with questions about drugs or procedures not considered

teratogenic were asked to enroll as controls. The study found that the proportion of liveborn infants with major structural anomalies was 3.6% in the exposed group and 1.0% in the control group (Relative Risk (RR) 3.59, 95% Confidence Interval (CI) 0.61-21.10). Three of the 83 women who had exposure in the first trimester of their pregnancies had infants with major structural anomalies, one with a cardiomyopathy, another with a muscular ventricular septal defect and small left colon syndrome, and the third with bilateral indirect inguinal hernias. The proportion of infants with at least three minor anomalies was 11.7% in the exposed group versus 7.6% in the control group (RR 1.53, 95% CI 0.61-3.82). There were no significant differences between groups in premature delivery (8.6% vs. 7.7%, $p=0.95$) or spontaneous pregnancy loss (6.1% vs. 8.2%, $p=0.65$). Statistically significantly higher birth weight (3710 vs. 3494 g, $p=0.001$), larger head circumference (35.2 vs. 34.6 cm, $p=0.02$), and a higher frequency of gestational diabetes (11% vs. 4%, $p=0.05$) were found in the exposed group.

3.1.2 OSE Comments

This study examined the effects of concomitant use of phentermine and fenfluramine in pregnant women. Therefore, the individual effect of phentermine on pregnancy outcomes cannot be assessed in this study. Secondly, because of the small sample size, this study was underpowered to detect any but the most dramatic increase in relative risk for a single major malformation. As the author pointed out that the study had 80% power to detect about a 9-fold or greater relative risk for all major structural defects combined (9% in exposed vs. 1% in unexposed) and a 3-fold or greater relative risk for at least 3 minor malformations (25% in exposed vs. 8% in unexposed). Another limitation, related to the generalizability of the study results, was that the study sample of exposed women may not be representative of all women who took phentermine and fenfluramine during pregnancy because the study subjects contacted the California Teratogen Information Service voluntarily. Fourth, major congenital anomalies that were prenatally diagnosed were excluded. As a result, this exclusion criterion may have underestimated the incidence of major congenital anomalies in study subjects and may have biased the findings toward the null. Lastly, the study did not provide the underlying conditions for patients in the exposed group and those in the control group, although phentermine and fenfluramine were often prescribed together for weight reduction during this period. It is

likely that the patients in the exposed and control groups differed by the underlying conditions, such as obesity, which may have had a confounding effect on the outcome measures. Despite these limitations, it is worth noting that congenital anomalies were more frequent, and birth weight, head circumference, and the occurrence of gestational diabetes were statistically significantly increased in the phentermine and fenfluramine exposed group compared to the control group.

3.2 TOPIRAMATE

This review identified three cohort studies and three case reports on adverse pregnancy outcomes with topiramate use. A brief summary and critique of each study are provided below.

3.2.1 Cohort Studies

3.2.1.1 Study Synopsis

Ornoy et al.¹⁰ reported pregnancy outcomes for 52 pregnancies with topiramate exposure who contacted the Israeli Teratogen Information Service (TIS) in regard to exposure to topiramate (indication unknown) between January 1996 and December 2006. The outcomes of those 52 pregnancies were compared with 212 pregnancies of women who contacted the TIS during the same time period and were exposed to non-teratogenic agents. The results showed that the rate of spontaneous abortions was considerably higher in the exposed group compared to the control group (11.3% vs. 2.8%, $p=0.017$) although the adjusted odds ratio was not statistically significant (adjusted odds ratio 3.07, 95% CI 0.8-11.8). Birth weight was significantly lower in the exposed group compared to the controls ($p=0.024$). The frequencies of induced abortions (9.4% vs. 3.8%) and ectopic pregnancies (1.9% vs. 0) were higher in the exposed group compared to the controls. Major anomalies were found in 4 offspring of exposed women (9.8%) compared to 3.4% of those of controls. The major anomalies associated with topiramate exposure included one case each of DiGeorge syndrome (genetic in origin), Prader Willi syndrome (genetic in origin), pulmonary artery stenosis (with topiramate monotherapy exposure), and multiple brain cysts with neonatal seizures (with topiramate combined with valproic acid and clonazepam exposures).

3.2.1.2 OSE Comments

With a sample size of 41 live births, this study did not permit the detection of mild to moderate risk of congenital anomalies associated with topiramate. Also, the magnitude of the differences in the frequencies of induced abortions, ectopic pregnancies, and major anomalies between the topiramate exposed and control groups could not be determined since the study did not report the 95% confidence intervals. Another limitation to this study is that the study subjects may not be representative of all women who had exposure to topiramate during pregnancies in Israel within the study time period since the study subjects chose to contact the TIS spontaneously. The study methods did not specify whether the 52 pregnancies analyzed in this study accounted for the total number of women who contacted the TIS regarding their exposure to topiramate during the study time. If not, the study failed to provide the criteria for sample selection. Lastly, the study did not provide the underlying conditions for patients in the exposed group and those in the control group. It is likely that the patients in the exposed and control groups differ by the underlying diseases which may have a confounding effect on the outcome measures.

3.2.1.3 Study Synopsis

A prospective observational study from the UK Epilepsy and Pregnancy Register was conducted during December 1996 and March 31 2005 to examine the rates of major congenital malformation (MCM) in women with epilepsy who had exposure to topiramate and other AEDs¹¹. The study reported that 7.1% of infants exposed to topiramate monotherapy (n=35) had a MCM with one case of cleft lip and palate and one case of hypospadias. Compared to epileptic women who were not exposed to any AEDs during their pregnancies, the adjusted OR of MCMs associated with topiramate monotherapy was 3.46 (95% CI 0.73-16.39).

3.2.1.4 OSE Comments

This study may underestimate the rate of MCM in the study population. However, it is unknown whether the magnitudes of underestimation differ between the topiramate monotherapy group and the control group of patients who were not exposed to any AEDs during their pregnancies. The sources of underestimation included that the study excluded pregnant women who had abnormal prenatal tests, those who had a pregnancy loss in

which an abnormality had been identified before referral to the register, and those who were not on AEDs during the first trimester but had second or third trimester AED exposure. Another source of underestimation was the short time frame for outcome identification. This study only recorded MCMs noted at birth or during the first six weeks of life. It is possible that some MCMs may present much later in life.

3.2.1.5 Study Synopsis

Hunt et al.¹² conducted another prospective observational study examining the pregnancy outcomes of first-trimester exposure to topiramate using the UK Epilepsy and Pregnancy Register data from December 1996 through August 31, 2007. The study reported that the rates of MCM and any malformation were 4.8% (95% CI 1.7-13.3%) and 12.9% (95% CI 6.7-23.4%), respectively, among 70 pregnancies exposed to topiramate monotherapy. The MCM with topiramate monotherapy identified in this study included one case each of cleft lip and bilateral cleft palate, hypospadias, and cleft lip and palate. Minor congenital malformation included sacral dimple, clicky hips, plagiocephaly, toe webbing, and immature hip joints. The rates of MCM and any malformation were 11.2% (95% CI 6.7-18.2%) and 19.8% (95% CI 13.6-28.0%), respectively, among 133 pregnancies who had taken topiramate as part of a polytherapy regimen during their first trimester for the treatment of epilepsy. The MCM associated with topiramate polytherapy included left hydronephrosis, pyloric stenosis (3 cases), hernia and hydrocele, anal atresia, tracheoesophageal fistula, hypospadias, cleft palate and crossed toes, congenital dislocated hips, and Harold type II talipes. The minor congenital malformations associated with polytherapy included glandular hypospadias, abnormality of foreskin, dysmorphic features, left ureteric reflux, patent ductus arteriosus, benign heart defect, mild hypospadias, cavernous hemangioma, clicky right hip, and intra-abdominal cyst.

3.2.1.6 OSE Comments

Similar to the Morrow study, this study may underestimate the rate of MCM associated with first trimester exposure to topiramate and other AEDs. The underestimation may be caused by the exclusion of pregnant women who had abnormal prenatal test and those who had a pregnancy loss in which an abnormality had been identified before referral to the register. Another source of underestimation was the short time frame for outcome

identification. This study only recorded MCM noted at birth or during the first six weeks of life. It is possible that some MCM may present much later in life. Lastly, this study did not assess the rate of MCM in women who had not exposed to topiramate during their first trimester of pregnancies. Therefore, it is unknown whether topiramate was associated with higher rate of MCM compared to non-exposed women with epilepsy. As a result, it is impossible to distinguish the drug effects from that of the underlying epilepsy condition in this study.

3.2.2 Case Reports

3.2.2.1 Study Synopsis

Gorman et al.¹³ reported that two cases of neonatal hypocalcemic seizures and transient hypoparathyroidism occurred to siblings of a mother who took topiramate 200 mg twice daily throughout the pregnancy. Case 1 started to have episodes of seizures on day 3 of life. Case 2 presented episodes of seizures on day 7 of life.

Ceren et al.¹⁴ reported that a neonate whose mother received topiramate 300 mg per day throughout pregnancy was born with agenesis of the right thumb, hypoplasia of the left thumb, syndactylia of the second and third toes of the foot with agenesis of some phalanges, and hypoplasia of the right orbicular muscle in the mouth.

In a review article, Yerby et al.¹⁵ reported that 5 cases of hypospadias occurred among 139 pregnancies (87 live births, 23 therapeutic abortions, 29 lost to follow-up) who had exposure to topiramate during pregnancy per personal communication at the Finnish Epilepsy Society Annual Meeting in 2002.

3.2.2.2 OSE Comments

These three case reports may be safety signals of congenital malformations associated with topiramate use in pregnant women. However, because of the anecdotal nature of case reports, no firm conclusion on the causal relationship can be made based on these cases.

3.3 PHENTERMINE & TOPIRAMATE

Relevant studies or reports on adverse pregnancy outcomes for concomitant use of phentermine and topiramate were not found in the current literature.

4 DISCUSSION

With the use of topiramate and phentermine in obesity women, the number of pregnancies with exposure to these two agents is expected to be much higher than currently. The potential teratogenic effects of topiramate, and possibly phentermine, may result in increased numbers of offspring with congenital malformations.

The congenital malformations associated with phentermine and topiramate use were varied and no obvious pattern was observed in the studies and case reports identified in the literature review. Adverse pregnancy outcomes associated with phentermine use reported in the cohort study identified in this review included cardiomyopathy, muscular ventricular septal defect, small left colon syndrome, and bilateral indirect inguinal hernias as identified in the Jones study⁹. Adverse pregnancy outcomes associated with topiramate use alone reported in published cohort studies and case reports included spontaneous abortions, induced abortions, ectopic pregnancies, low birth weight, major congenital malformations of pulmonary artery stenosis, multiple brain cysts with neonatal seizures, neonatal hypocalcemic seizures, cleft lip and palate, hypospadias, and agenesis of the thumb and phalanges, and minor congenital malformations of sacral dimple, clicky hips, plagiocephaly, toe webbing, and immature hip joints. There are no data on adverse pregnancy outcomes associated with concomitant use of phentermine and topiramate.

Despite the reported congenital anomalies associated with phentermine and topiramate use, only a limited number of publications were available in the literature, and each study identified in this review had significant limitations. Therefore, the magnitude and absolute risk of congenital anomalies associated with topiramate and phentermine use alone or in combination is not known.

5 CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the literature suggests that topiramate and phentermine use may be associated with an increased risk of congenital malformation. However, the magnitude and absolute risk of congenital anomalies associated with topiramate and phentermine use alone or in combination cannot be determined based on the limited published data.

To avoid the potential drug-associated risk of congenital anomalies and to comply with the general recommendation of not attempting to lose weight while pregnant, we do not

recommend the use of phentermine and topiramate in combination for the treatment of obesity in pregnant women.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

JING JU
06/18/2010

DIANE K WYSOWSKI
06/18/2010

TAREK A HAMMAD
06/18/2010



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

Date: June 17, 2010

To: Mary Parks, MD
Director, Division of Metabolic and Endocrine Products (DMEP)
Office of Drug Evaluation II, Office of New Drugs, CDER

From: Jo Wyeth, PharmD
Safety Evaluator, Division of Pharmacovigilance (DPV) I
Office of Surveillance and Epidemiology (OSE), CDER

Through: Mark Avigan, MD, CM
Associate Director, Office of Surveillance and Epidemiology (OSE)
Acting Director, Division of Pharmacovigilance (DPV 1), OSE

Lanh Green, PharmD, MPH
Safety Evaluator Team Leader, Division of Pharmacovigilance (DPV) I
Office of Surveillance and Epidemiology (OSE), CDER

Subject: AERS Review

Drug Name(s): Phenteramine/Topiramate (Qnexa)

Application
Type/Number: NDA 22-580

Applicant/sponsor: Vivus, Inc

OSE RCM #: 2010-500

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

JO H WYETH
06/17/2010
Change made on page 5

MARK I AVIGAN
06/17/2010



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

Date: June 7, 2010

To: Mary Roberts, MD, Medical Officer
Division of Metabolic and Endocrinology Products
Office of New Drugs

Through: Amarilys Vega, MD, MPH/ Deputy Director
Division of Epidemiology
Office of Surveillance and Epidemiology

Laura Governale, Pharm.D., MBA
Drug Use Analyst Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Vicky Borders-Hemphill, Pharm.D.
Drug Use Data Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: Phentermine Concurrency with Topiramate

Drug Name(s): Phentermine (Adipex-P and generic) and Topiramate
(Topamax[®] and generic)

Application Type/Number: ANDA 85-128, ANDA 88-023 and various; NDA 20-505, and
NDA 20-844

Applicant/sponsor: Teva and Ortho McNeil Janssen

OSE RCM #: 2010-500

EXECUTIVE SUMMARY

The Division of Metabolism and Endocrinology Products (DMEP) is reviewing an NDA 22-580 for Qnexa (phentermine/topiramate) that was submitted on December 28, 2009 by Vivus, Inc. for the treatment of obesity, including weight loss and maintenance of weight loss. An Advisory Committee meeting is scheduled for July 15, 2010. This review provides an analysis of concurrent phentermine and topiramate use in a sample of patients as well as estimates of national utilization of each drug.

Concurrency Analysis: Data from VOCON are non-projected patients counts. Nationwide projections are not available.

- In the non-projected sample of patients used to assess concurrency during years 2007 through 2009:
 - Approximately (b) (4) patients filled a phentermine prescription and (b) (4) patients filled a topiramate prescription during the study period.
 - Overall, there was low concurrent use between the two products. Approximately 3.2% of patients filling a prescription for phentermine (b) (4) concurrently filled a prescription for topiramate; alternatively, 3.5% of topiramate patients concurrently filled a prescription with phentermine.

National Utilization Estimates: Data from VONA are projected national estimates.

- Sales data for topiramate, year 2009, indicated that approximately (b) (4) of topiramate tablets and capsules and (b) (4) of phentermine tablets and capsules were distributed to outpatient retail pharmacies.
- In year 2009, an estimated (b) (4) topiramate and (b) (4) phentermine prescriptions were dispensed nationally in the outpatient retail pharmacy settings.
- Topiramate prescriptions have steadily increased over time since approval. The data suggests that topiramate use for weight control represents a relatively small proportion of the use. Reports of diagnoses associated with the use of topiramate for the treatment of obesity included ICD-9 307.5 EATING DISORDERS NEC/NOS (at (b) (4) of mentions) and ICD-9 278.0 OBESITY (at (b) (4) of mentions).
- Over the past 19 years, the number of dispensed phentermine prescriptions peaked during year (b) (4) and then dramatically decreased during year (b) (4) and continued to fall steadily through to year (b) (4). Dispensed phentermine prescriptions have increased (b) (4) from year (b) (4).

1 INTRODUCTION

The Division of Metabolism and Endocrinology Products (DMEP) is reviewing an NDA 22-580 for Qnexa, a phentermine/topiramate combination product that was submitted on December 28, 2009, by Vivus, Inc. for the treatment of obesity, including weight loss and maintenance of weight loss. Qnexa should be used in conjunction with diet and exercise and is recommended for 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 such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity). An Advisory Committee meeting is scheduled for July 15, 2010, to discuss the safety and efficacy. In support of this review, the Division of Epidemiology (DEPI) conducted an analysis of concurrent use phentermine and topiramate. In addition, we examined the nationally projected number of total dispensed prescriptions for phentermine and topiramate during years 1991 through 2009 to gain a sense of the national utilization of these products. Physician reports of diagnoses associated with the use of Topamax® were also analyzed.

2 BACKGROUND

Phentermine is an anorexigenic agent used as an adjunct to exercise, behavioral modification, and caloric restriction in the short-term management of exogenous obesity. As a resin complex, phentermine was originally approved in May 1959 as Ionamin (UCB Inc.) but this extended-release formulation has been discontinued. Phentermine HCl was originally approved in August 1973 as Fastin (GlaxoSmithKline) and has also been discontinued. It is currently available as Adipex-P 37.5 mg (capsules approved August 1983 and tablets approved October 1980). Various phentermine generics are available as well.

Topiramate (Topamax®) is an antiepileptic agent indicated for initial monotherapy in patients ≥ 10 years of age with partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥ 2 years of age with seizures associated with Lennox-Gastaut syndrome, and treatment for adults for prophylaxis of migraine headache. Topamax® tablets were approved December 1996 and capsules were approved October 1998. It is available as 25 mg, 50 mg, 100 mg, 200 mg tablets and 15 mg, 25 mg capsules.

3 METHODS AND MATERIAL

3.1 DETERMINING SETTINGS OF CARE

We used outpatient drug utilization databases to assess phentermine and topiramate utilization because sales data for year 2009 indicated that approximately (b) (4) of topiramate tablets and capsules were distributed to outpatient retail pharmacies; (b) (4) were to mail order pharmacies, and (b) (4) to non-retail settings. For phentermine tablets and capsules, approximately (b) (4) were distributed to outpatient retail pharmacies; (b) (4) were to mail order pharmacies, and (b) (4) to non-retail settings.¹ Neither mail order nor non-retail settings were included in this analysis.

1 IMS Health, IMS National Sales Perspectives™, Year 2009, Extracted 4-23-10. File: 1004TOP.dvr

3.2 DATA SOURCES USED

3.2.1 Concurrency Analysis

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

The SDI Vector One[®]: Concurrency (VOCON) tool was used to estimate the number of patients who filled a prescription for phentermine concurrent with topiramate from January 2007 through December 2009.

One report was generated from concurrency scenarios using the following criteria. An episode of concurrency is identified when a prescription in the Base group, phentermine, overlaps with the days supply for a dispensed prescription for drugs in the Concurrent group, topiramate. The days supply is calculated by adding the number of *therapy days* to the time of prescription dispensing. A grace period of 50% is allowed for the days supply time window to adjust for delays in prescription filling. Thus, the total days of therapy for a claim with 30 days supply would be 45 days when including the 50% grace period. The number of *therapy days* is estimated by dividing the number of tablets or capsules dispensed by the number of tablets or capsules consumed per day. Data from VOCON are unprojected patients counts. Nationwide projections are not available for concurrency analyses.

3.2.2 Nationally projected outpatient dispensed prescriptions and provider prescribing practices

We also examined nationally projected number of total dispensed prescriptions for phentermine and topiramate using SDI Vector One[®]: National (VONA). Reports of diagnoses associated with the use of topiramate or Topamax[®] were obtained from the SDI's Physician's Drug and Diagnosis Audit[™] (PDDA) from years 1991 through 2009.

4 RESULTS: DATA

4.1 CONCURRENCY BETWEEN PHENTERMINE AND TOPIRAMATE

Tables 1 (see Appendix 1) provides data showing the extent of concurrency between phentermine and topiramate from January 2007 through December 2009. In this sample of patients, approximately (b) (4) patients filled a phentermine prescription and (b) (4) patients filled a topiramate prescription during the study period. Overall, there was low concurrent use between the two products. Approximately, 3.2% of patients filling a prescription for phentermine (b) (4) concurrently filled a prescription for topiramate. Alternatively, approximately 3.5% of topiramate patients concurrently filled a prescription with phentermine.

4.2 NATIONALLY PROJECTED NUMBER OF OUTPATIENT DISPENSED PHENTERMINE AND TOPIRAMATE PRESCRIPTIONS (FIGURE 1)

In year 2009, an estimated (b) (4) topiramate and (b) (4) phentermine prescriptions were dispensed nationally in the outpatient retail pharmacy settings. Topiramate prescriptions have steadily increased over time since approval. Over the past 19 years, the number of dispensed phentermine prescriptions peaked during year (b) (4) and then dramatically decreased during year (b) (4) and continued to fall steadily through to year (b) (4). Dispensed phentermine prescriptions have increased (b) (4).

4.3 DIAGNOSES ENCOUNTERED IN THE OFFICE-BASED PRACTICE SETTING

According to office-based physician practices in the U.S. from January 1991 to December 2009, top diagnosis codes associated with the use of topiramate are listed in Table 2. Reports of diagnoses associated with obesity included ICD-9 307.5 EATING DISORDERS NEC/NOS (at (b) (4) of mentions) and ICD-9 278.0 OBESITY (at (b) (4) of mentions) for topiramate during the time period studied.

5 DISCUSSION

The findings from this consult should be interpreted in the context of the known limitations of the databases used. When examining concurrency in the VOCON tool, several assumptions are made: (1) that a patient is taking the prescription(s) as recommended; and (2) the days supply for a prescription is recorded to reflect how the patient is actually taking the prescription.

SDI's Vector One[®]: Concurrency does not capture data from mail order pharmacies. Mail order pharmacies typically dispense chronic use meds in larger quantities than retail pharmacies. We therefore believe that the omission of mail order may underestimate the days of concurrent therapy. Although the concurrency data presented in this review are all based on analysis of **unprojected patient** counts and they cannot be generalized to the national level, the SDI database is capturing a very large sample representing roughly half the retail prescription volume in the U.S.

We estimated that these products are distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives[™]. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

SDI's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data estimates unstable, particularly if use is not common in the pediatric population. SDI recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

6 CONCLUSIONS

Sales data for topiramate, year 2009, indicated that approximately (b) (4) of topiramate tablets and capsules and (b) (4) of phentermine tablets and capsules were distributed to outpatient retail pharmacies. During year 2009, an estimated (b) (4) topiramate and (b) (4) phentermine prescriptions were dispensed nationally, in the outpatient U.S. pharmacy setting.

Topiramate prescriptions have steadily increased over time since approval. The data suggest that topiramate use for weight control represents a relatively small proportion of its use. Reports of diagnoses associated with the use of topiramate for the treatment of obesity included ICD-9 307.5 EATING DISORDERS NEC/NOS (at (b) (4) of mentions) and ICD-9 278.0 OBESITY (at (b) (4) of mentions).

Over the past 19 years, the number of dispensed phentermine prescriptions peaked during year (b) (4) and then dramatically decreased during year (b) (4) and continued to fall steadily through to year (b) (4). Dispensed phentermine prescriptions increased (b) (4).

There was low concurrent use between phentermine and topiramate. Approximately 3% of patients that filled a phentermine prescription concurrently filled a prescription for topiramate.

CONCURRENCE

Laura Governale, Pharm.D., MBA, /Drug Use Analyst Team Leader
Division of Epidemiology (DEPI)
Office of Surveillance and Epidemiology
Amarilys Vega, MD, MPH/ Deputy Director
Division of Epidemiology (DEPI)
Office of Surveillance and Epidemiology

APPENDICES: APPENDIX 1. TABLES AND FIGURES

Table 1. Total Number of Patients on Concurrent Therapy with Phentermine and Topiramate from January 2007 through December 2009

Patients (Phentermine)	Patients (Topiramate)	Total Patients (in Phentermine OR Topiramate Group)	Total Patients (in Phentermine AND Topiramate Groups)	Concurrent Patients	Concurrent Patient % (Phentermine)	Concurrent Patient % (Topiramate)	TRx (Phentermine)	TRx (Topiramate)
(b) (4)								

Table 2. Office Based Physician-Reports of Diagnosis Encountered in the Office-Based Practice Setting

(b) (4)



Figure 1.

Projected Number of Dispensed Prescriptions for Phentermine or Topiramate, Years 1991-



(b) (4)

SDI Vector One®: National (VONA). Data extracted 5-17-10.
File: VONA 2010-500 phentermine topiramate Trx 1991-2009.xls

APPENDIX 2: DATABASE DESCRIPTION

SDI Vector One®: Concurrency (VOCON)

Data used in VOCON is derived from SDI's Vector One® database. The Vector One® database integrates prescription activity from a variety of sources, including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over (b) (4) prescription claims annually, representing over (b) (4) unique patients. Vector One® receives approximately half the of retail prescriptions dispensed nationwide. SDI obtains all prescriptions from approximately one-third of the reporting stores and a significant sample of prescriptions from the remaining stores.

VOCON allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period using four scenarios. These scenarios are (in order of most to least restrictive): Same day fills, overlapping days supply, overlapping days supply with % grace period, fills during the same time period.

The VOCON module provides unprojected patients counts. Nationwide projections are not available.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over (b) (4) prescription claims per year, representing over (b) (4) unique patients. Since 2002 Vector One® has captured information on over (b) (4) prescriptions representing (b) (4) unique patients.

Prescriptions are captured from a sample of approximately (b) (4) pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Physician Drug & Diagnosis Audit (PDDA)

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

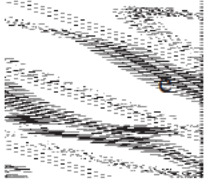
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

BRENDA V BORDERS-HEMPHILL
06/07/2010

AMARILYS VEGA
06/07/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff - Maternal Health Team Review

Date: June 2, 2010 **Date Consulted:** April 14, 2010

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: Qnexa (phentermine/topiramate) Controlled Release Capsules, NDA 22-580

Subject: MHT Review of Qnexa

Materials Reviewed:

- Reproductive Risk databases:
 - REPROTOX[®]
 - TERIS (the Teratogen Information Service)
- LactMed (the Drugs and Lactation Database)
- Draft Qnexa Labeling, submitted December 28, 2009
- Draft Proposed Qnexa REMS, submitted December 28, 2009, revised May 24, 2010

Consult Question: DMEP requests MHT input for Qnexa on the following:

- Labeling for pregnancy (including pregnancy category classification) and nursing mothers subsections
- Development of a pregnancy exposure registry
- Possible clinical lactation study
- Development of a pregnancy prevention plan

24 Pages Have Been Withheld As A Duplicate
Copy Of The Maternal Health Team Review Which
Is Located In the 2010 Advisory Committee
Meeting Materials

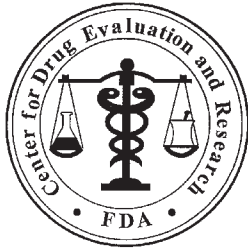
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/s/

JEANINE A BEST
06/02/2010

Karen B FEIBUS
06/02/2010
I agree with the content and recommendations contained in this review.

LISA L MATHIS
06/02/2010



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

Date: June 1, 2010

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products

Through: Melina Griffis, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Qnexa (Phentermine and Topiramate) Capsule, 3.75 mg/23 mg,
7.5 mg/46 mg, 11.25 mg/69 mg, 15 mg/92 mg

Application Type/Number: NDA 022580

Applicant/sponsor: Vivus, Inc

OSE RCM #: 2010-129

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1 INTRODUCTION

The Division of Medication Error Prevention and Analysis evaluated the proposed container label, carton labeling and insert labeling for Qnexa Capsules (NDA 22580) and identified vulnerabilities that could lead to medication errors.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA),¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling submitted as part of the December 28, 2009 original NDA submission. See Appendix A and B for images of proposed container labels and carton labeling.

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed container labels, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We request the recommendations for the container labels and carton labeling in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Margarita Tossa, at 301-796-4053.

3.1 COMMENTS TO THE DIVISION

- A. The dosage form (b)(4) is not a recognized dosage form in the USP. Thus, we defer to clinical pharmacology or ONDQA for the final determination of the dosage form.
- B. The strength should appear with the 'mg' designation following each number, e.g. 3.75 mg/23 mg, throughout the package insert.

3.2 COMMENTS TO THE APPLICANT

- A. Qnexa Container Label (All Strengths)
 - 1. Include the Medication Guide statement in accordance with 21 CFR 208.24(2)(d). We consider prominent and conspicuous display of the Medication Guide to be placed on the principal display panel.
 - 2. Relocate the Control Substance 'CIV' designation to appear after the dosage form so that there is no intervening matter between the established name and dosage form.
 - 3. The strength should appear with the 'mg' designation following each number, e.g. 3.75 mg/23 mg.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

ANNE CRANDALL
06/04/2010

MELINA N GRIFFIS
06/04/2010

DENISE P TOYER
06/04/2010

CAROL A HOLQUIST
06/04/2010

CONSULTATION REVIEW

NDA 22580 (505B2)

Drug: Qnexa (phentermine + topiramate)

Sponsor: Vivus, Inc

Indication: Anti- obesity (Combination centrally acting appetite suppressant)

Request for consultation from: Pat Madara, DMEP White Oak, bldg 22

Date of the request: March 10, 2010

Subject of consultation: A consult request “for adverse pregnancy outcomes in AERS database such as congenital anomalies associated with the use of topiramate and phentermine separately and co-administered”.

Reviewer: Sonia Tabacova, MD, Ph.D.

Division: Psychiatry Products

Review date: May 26, 2010

Phentermine (schedule IV): sympathomimetic amine, action is thought to be via norepinephrine reuptake inhibition and inhibition of monoamine oxidase subpart A activity; currently approved for short-term weight loss;

Topiramate: sulfamate-substituted monosaccharide that is believed to block voltage dependent sodium channels, augment the activity of gamma-aminobutyrate at GABA-A receptors, antagonize the AMPA/kinase subtype of the glutamate receptor, and inhibit the carbonic anhydrase enzyme. Weight loss is via an unknown mechanism.

Adverse developmental events reported to FDAs AERS in association with topiramate and phentermine gestational exposures

Topiramate (Topamax)

A total of 115 spontaneous reports of adverse fetal, neonatal and/or postnatal events associated with administration of topamax as a monotherapy to pregnant women were retrieved from FDA’s Adverse Event Reporting System (AERS) by Dr. Ana Szarfman. Out of these, 39 reports were excluded from this review because of the following reasons: duplicate reports (n=25); irrelevant reports (topiramate exposures not gestational/prenatal) (n=13); and outcome of pregnancy not reported (n=1). The remaining 76 case reports are the subject of this review.

Reporting sources: Out of the reviewed 76 reports, 23 originated in the U.S.; the majority (56, or about 70%) were from other countries. About a third of all reports (22 of 76) were from literature sources. Most of the reports (62 of 76, or over 80%) were from health professionals that supports their credibility.

The reported adverse events took place over the period from 1997 through 2009 (incl.)

Indication: Information about topamax indication was available in 51 reports. In 92% of these (47 of 51) topamax was used in pregnancy for treatment of maternal epilepsy; in only 4 cases the indication was migraine in pregnancy. No concurrent maternal diseases were reported except for 3 cases of pregnancy complications (premature rupture of membranes; amnionitis) and 1 case of pre-existing disease (brain tumor, surgically removed before conception). Thus, in the majority of cases there was uniformity of the maternal health background.

Administration and doses: Generally, topamax was administered as a monotherapy. Concomitant medication with other drugs was reported in only 5% of the cases (4 of 76), including: carbamazepine (in 2 cases, both during the 1st trimester); lamotrigine (in 1

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/s/

AISAR H ATRAKCHI
06/09/2010

THOMAS P LAUGHREN
06/09/2010

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	006 -2010
APPLICATION NUMBER	N22580
LETTER DATE/SUBMISSION NUMBER	S#000 and 018
PDUFA GOAL DATE	July 15, 2010 (AC meeting); Oct. 28, 2010
DATE OF CONSULT REQUEST	Jan. 14, 2010
REVIEW DIVISION	DMEP
MEDICAL REVIEWER	Mary Roberts, MD
REVIEW DIVISION PM	Patricia Madara and Pooja Dharja
SEALD REVIEWER(S)	June Cai, MD
REVIEW COMPLETION DATE	May 26, 2010
ESTABLISHED NAME	VI-0521
TRADE NAME	Onexa
APPLICANT	Vivus, Inc.
ENDPOINT(S) CONCEPT(S)	Quality of life
INSTRUMENT(S)	Quality of life questionnaires: 1) IWQOL-Lite; 2) SF-36
INDICATION	Long-term treatment of obesity
INTENDED POPULATION(S)	Obese patients

STUDY ENDPOINT REVIEW

A. EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrinology Products regarding NDA# 22580.

The review concludes that neither of the PRO instruments in this NDA (b) (4) was specified primary or key secondary endpoints. Even if IWQOL- Lite in OB-301 was counted as part of secondary endpoints, examination of its items shows problematic content validity just as concluded in previous SEALD reviews of this instrument. Inadequate content validity will result in problems in interpreting the results measured by this scale. Examples of content validity issues include:

- Some items included in the Physical Function score (swollen ankles and lower legs as well as worry about health) don't represent Physical Function
- Many items of other subscales (Self-esteem, Sexual Life, Public Distress, and Work) represent concepts that result from the impact of obesity/weight problems but are also a result of the impact of many other factors in life.

Finally, since PRO measures were only exploratory endpoints of OB-302 (EQUIP) and OB-303 (CONQUER), (b) (4)

B. STUDY ENDPOINT REVIEW

Vivus, Inc. submitted this NDA using Onexa (phentermine and topiramate) as long term treatment of obesity under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act on Dec. 28, 2009. DMEP submitted the consult on Jan. 14, 2010 but with no specific questions other than asking SEALD to review instruments of quality of life. Filing meeting was on Feb. 22, 2010. (b) (4)

On April 7, 2010, the DMEP sent out the following request: "Please submit user manuals for the IWQOL-Lite and SF-36 instruments. In order to evaluate these instruments, we require you to submit more detailed materials for each instrument (b) (4). These materials include a conceptual framework of the instrument, content validity documentation, assessment of construct validity, reliability, and ability to detect change." On the evening of April 29, 2010, the sponsor sent in the response which will be reviewed below.

STUDY ENDPOINT REVIEW

This application has a PDUFA date of Oct. 28, 2010, a wrap-up meeting scheduled on Sept. 22, 2010, and an AC meeting planned for July 15, 2010.

Prior to the submission, there were three protocol amendments (October, November, and December 2007). However, the changes did not affect PRO endpoints or the hierarchy of study endpoints.

1 INSTRUMENT(S)

The two instruments used (b) (4) are 1) IWQOL-Lite and 2) SF-36.

1) IWQOL-Lite (Impact of Weight on Quality of Life Questionnaire – Lite Version)

This instrument is a 31-item self administered instrument that includes 5 domains: Physical function, public distress, sexual life, self-esteem, and work. Each domain contains 4 - 11 questions and each question scores on Likert scale from “never true (1)” to “always true (5)”. Recall period is one week (“in the past week”). It is displayed in Appendix 1 of this review. In the protocol of OB-301, this instrument was listed for being administered at Screening and at study completion (Week 28 or early termination).

The sponsor didn’t submit the former version (or non-lite) version of this instrument.

2) SF-36:

This is a 36-item, self-administered questionnaire designed to evaluate functional health and well-being. Each question has its own Likert scale as response option. Items are grouped into 10 questions with additional question (Q10) added in Version 2.0 that inquires if one’s physical or emotional health had prevented his/her social activities, such as visiting friends or relatives in the past four weeks. The copy of the questionnaire is attached in Appendix 2 of this review.

It was completed by subjects at Screening (Visit 1a), Visit 10 (Week 28), and at the end of treatment (Visit 17, i.e. Week 56 or early withdrawal).

For both instruments, the protocol specifies that staff would not interpret anything to the patient when asked, and that no missing answers could be queried and filled out at a later time.

Reviewer’s Comment: Upon request for more information including user manual and materials regarding training, the sponsor submitted four published articles to support each instrument. Since SF-36 is one of the exploratory endpoints, this review will only focus on IWQOL-Lite that was used as one of the secondary efficacy endpoints.

2 TARGET PRODUCT PROFILE

There is no formal submission of TPP.

The following is listed in the proposed **INDICATIONS AND USAGE** section: QNEXA is indicated 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 ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight patients ($\text{BMI} \geq 27 \text{ kg/m}^2$) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

(b) (4)

3 ENDPOINT MODEL

PRO instruments were used in three pivotal phase 3 studies, OB-301, 302, and 303. IWQOL-Lite is listed as one of the secondary endpoints of OB-301 only; it is listed as one of “other” endpoints in OB-302 (EQUIP) and, together with SF-36, in OB-303 (CONQUER). The hierarchy of endpoints was not changed in the protocol amendments. The table below summarizes the endpoints of these three trials.

STUDY ENDPOINT REVIEW

Table 1. Endpoint Models of Phase 3 Studies OB-301, 302, and 303

	OB-301	OB-302 (EQUIP)	OB-303 (CONQUER)
Phase 3 Study Title	A randomized, double-blind, parallel-design study comparing multiple doses of VI-0521 to placebo and their single-agent phentermine and topiramate constituents for the treatment of obesity in adults	A randomized, double-blind, placebo-controlled, multicenter study to determine the safety and efficacy of VI-0521 in the treatment of obesity in an adult population with body mass index $\geq 35 \text{ kg/m}^2$	A randomized, double-blind, placebo-controlled, multicenter study to determine the safety and efficacy of VI-0521 in the treatment of obesity in adults with obesity-related co-morbid conditions
Primary Endpoints	1) Percent of weight loss at Week 28 2) Percentage of subjects achieving at least 5% weight loss at Week 28.	1) Percent weight loss at Week 56 2) Percentage of subjects with at least 5% weight loss at Week 56.	
Secondary Endpoints ^a	1) The proportion of subjects achieving 10% weight loss 2) changes from baseline to Week 28 in waist circumference 3) IWQOL domain and composite scores	1) Absolute weight loss at Week 56 2) Percentage of subjects with at least 10% weight loss at Week 56 3) Change in waist circumference from baseline to Week 56	
Other Endpoints	Visual analog scale assessments of hunger and satiety, change in the Framingham 10-year risk assessment, percent changes in lipids, changes in hemoglobin A _{1c} (HbA _{1c}) and fasting blood glucose, and changes in SBP and DBP.	Changes in Impact of Weight on Quality of Life (IWQOL)-Lite scores , change in BMI, percentage of subjects with at least 15% weight loss, changes in SBP and DBP, percent changes in lipids, change in fasting serum glucose, visual analog scale assessments of hunger and satiety, and changes in percent adiposity and percent lean body mass as measured by dual energy X-ray absorptiometry (DEXA) (selected sites only).	
			Changes in SF-36 scores , changes in HbA _{1c} and fasting insulin

a: The sponsor did not designate any of them as the “key” secondary endpoint(s).

Reviewer’s Comment: Given the roles of IWQOL-Lite and SF-36 in trials EQUIP and CONQUER, (b) (4) Thus, SF-36 will not be reviewed furthermore. (b) (4)

4 CONCEPTUAL FRAMEWORK

The sponsor didn't not submit conceptual framework for either of the instruments.

5 CONTENT VALIDITY

The sponsor didn't submit any qualitative study materials such as protocols and interview guides. Instead, the sponsor submitted two articles on initial development (see 1 and 2 of Section 9 Key References) of the scale and two papers on other psychometric evaluations including construct validity.

Reviewer's Comment: SEALD previously reviewed IWQOL-Lite for two IND's that studied patients with diabetes (see 3 and 4 of Section 9 Key References). However, some general comments regarding the scale apply here as well: (b) (4)

Previous SEALD review also pointed out the concern for recall period: "The one-week recall period presents interpretation difficulties." "Published literature documents that people do not actually have access to an unbiased memory of experiences, much information is simply no longer available to the individual, and the circumstances under which the recall task is conducted can affect the accessibility of the information. Moreover, memories are often distorted. In general, we advocate a much shorter recall period."

Item 10 of the same subscale, "My ankles and lower legs were swollen at the end of the day" does not represent a physical function; rather, it depicts the physical status of the ankles and lower leg. Additionally, as pointed out previously, item number 11 from the IWQOL- Lite, Physical Function subscale, "I am worried about my health", is not a measure of physical function or "decreased physical impairment due to Obesity". Inclusion of these items in a scale score would result in misleading and difficulty in interpretation of the scale.

Moreover, many items in the other four subscales of Self-esteem, Sexual Life, Public Distress, and Work can also frequently be affected by psychological factors beyond weight/obesity problem; these make it hard to prove weight/obesity as the only attribute for these difficulties in patients' life. To really make the proof, one would also have to provide the positive challenge (i.e. these issues get worse again when patients regain their weight).

Of interest, a previous SEALD consultative review also pointed out that in the original publication, a comparison of pre- and post-treatment scores on the IWQOL showed that although the impact of weight generally worsened as the patients' size increased, there was no association between BMI and impact of weight on Self-Esteem and Sexual Life in women. Even at the lowest BMI tertile studied, women reported that weight had a substantial impact in these areas. There were also other significant gender differences, with women showing greater impact of weight on Self-Esteem and Sexual Life compared with men.

In summary, the content validity of IWQOL-Lite is problematic

(b) (4)

6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Due to problems in content validity of the scale, assessment of these measurement properties is meaningless.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

All three Phase 3 pivotal studies were conducted in the United States. Therefore, translation to other language is not required.

8 PROTOCOL AND ANALYSIS PLAN

OB-301 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, factorial study in obese adults, which compared full-dose and mid-dose VI-0521 with placebo and the respective single-agent PHEN and TPM components after 28 weeks of treatment.

The study population included adult subjects ≤ 70 years of age with a BMI ≥ 30 kg/m² and ≤ 45 kg/m². Subjects with type 2 diabetes were excluded from participation. Eligible subjects were assigned randomly to receive daily treatment with placebo, PHEN 7.5 mg, PHEN 15 mg, TPM 46 mg, TPM 92 mg, PHEN/TPM 7.5/46 mg, or PHEN/TPM 15/92 mg capsules. A similar number of subjects were randomized to each treatment. Randomization was stratified by gender to ensure a similar distribution of male and female subjects across the treatment groups.

Statistic analysis plan of OB-301 is summarized in synopsis as the following:

“The primary analysis set for efficacy was the Intent-to-Treat (ITT) Set, defined as all randomized subjects who provided a baseline measurement of body weight, received at least one dose of study drug, and had at least one post-dose assessment of body weight. The primary endpoint for efficacy analyses was Week 28 with LOCF; for these analyses, the last post-dose measurement was used, regardless of whether or not the subject was on study drug.

Analysis of the first primary efficacy variable, percent weight loss at Week 28 with LOCF, was performed using an analysis of covariance (ANCOVA) model with treatment and gender as fixed effects and baseline weight as a covariate. For each treatment comparison of interest, the difference in least-squares (LS) means, corresponding standard error, two-sided 95% confidence interval, and two-sided p-value were derived from the ANCOVA model. Analysis of the second primary efficacy variable, percentage of subjects with at least 5% weight loss at Week 28 with LOCF, was performed using a logistic regression model with treatment and gender as fixed effects and baseline weight as a covariate. For each treatment

STUDY ENDPOINT REVIEW

comparison of interest, the estimated odds ratio (OR), standard error, 95% Wald confidence interval, and p-value were derived.

The same methodology for the analysis of percent weight loss at Week 28 with LOCF was used for the analysis of changes in waist circumference and IWQOL composite and domain scores from baseline to Week 28 with LOCF. The IWQOL scores were mapped to a 0 to 100 scale by subtracting the observed score from the maximum value for the component, dividing by the range for the component, and multiplying by 100.

The same methodology for the analysis of percentage of subjects with at least 5% weight loss was used for the analysis of percentage of subjects with at least 10% weight loss at Week 28 with LOCF.”

9 KEY REFERENCES FOR INSTRUMENT

1. Kolotkin RL, Head S, Hamilton MA, Tse CTJ. Assessing impact of weight on quality of life. *Obes Res.* 1995;3:49-56
2. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obes Res.* 2001;9:102-111
3. SEALD consultative review on IND (b) (4)
4. SEALD consultative review on IND# (b) (4).
5. FDA Guidance for Industry – Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009

C. APPENDICES

1. IWQOL-Lite (Impact of Weight on Quality of Life Questionnaire – Lite Version):

Please answer the following statements by circling the number that best applies to you in the past week. Be as open as possible. There are no right or wrong answers.

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STUDY ENDPOINT REVIEW

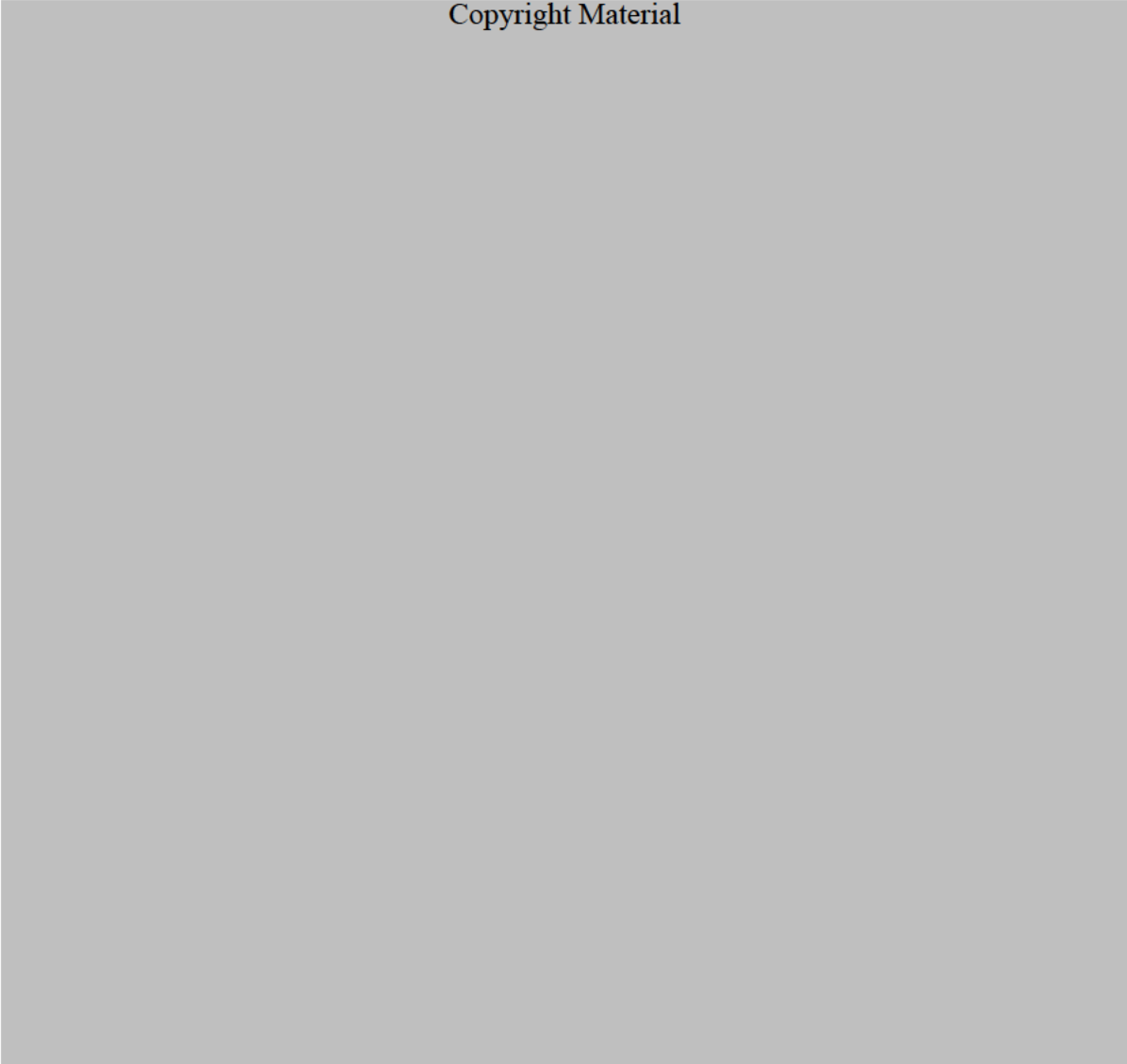
Copyright Material



2. SF-36 (Continue on next page)

Your Health and Well-Being

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(SF-36v2 Standard, US Version 2.0)

STUDY ENDPOINT REVIEW

Copyright Material



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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

/s/

JUNE CAI
05/25/2010

LAURIE B BURKE
05/25/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22580 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Qnexa Established/Proper Name: phentermine + topiramate Dosage Form: capsule Strengths: 3.75mg/23mg; 7.5mg/46mg; 11.25/69; 15/92		
Applicant: Vivus, Inc. Agent for Applicant (if applicable):		
Date of Application: 12/28/09 Date of Receipt: 12/28/09 Date clock started after UN: N/A		
PDUFA Goal Date: October 28, 2010	Action Goal Date (if different):	
Filing Date: February 26, 2010	Date of Filing Meeting: February 22, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s): 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 ³ 30 kg/m ²), or overweight patients (BMI ³ 27 kg/m ²) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<div style="display: flex; flex-direction: column;"> <div> <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) </div> <div> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) </div> </div>	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 68651				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified: N/A			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small.				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm	X Qnexa is for a new indication			
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
20505	Topamax	PED(method of use patent)	6/22/2013	
20505	Topamax	M54(method of use patent)	12/22/2012	
20844	Topamax	PED, M-54	As above	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting</i>	XX			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) X All electronic <input type="checkbox"/> Mixed (paper/electronic) X CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance¹?</p> <p>If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p>X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	X			
<p>Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i> 12/30/09</p>	X			
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>			X	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>		X		requested
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	X			
<i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	X Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) X Medication Guide (MedGuide) X Carton labels X Immediate container labels <input type="checkbox"/> Diluent X Other (b) (4)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	X			
<i>If no, request in 74-day letter.</i>				
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?			XX	
<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	XX			Will review when Substantially complete
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	XX			
REMS consulted to OSE/DRISK?	XX			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?				
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)				
<i>If yes, specify consult(s) and date(s) sent:</i>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	XX			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	XX			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	XX			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 22, 2010

BLA/NDA/Supp #: 22580

PROPRIETARY NAME: Qnexa

ESTABLISHED/PROPER NAME: immediate-release phentermine hydrochloride beads and modified-release topiramate beads formulated for oral administration.

DOSAGE FORM/STRENGTH: Capsules: 3.75mg/23 mg, 7.5mg/46 mg, 11.25mg/69 mg, 15mg/92 mg phentermine / topiramate.

APPLICANT: Vivus, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): 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 \geq 30 kg/m²), or overweight patients (BMI \geq 27 kg/m²) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pooja Dhaira (initially – P.Madara)	Y
	CPMS/TL:	Lina Aljuburi	Y
Cross-Discipline Team Leader (CDTL)	Eric Colman		Y
Clinical	Reviewer:	Mary Roberts	Y
	TL:	Eric Colman	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	

Clinical Pharmacology	Reviewer:	Johnny Lau	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Lee Ping Pian	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Carlson	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	TBD	N
	TL:	TBD	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Joseph Leginus	N
	TL:	Su Tran	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	TBD	
	TL:	TBD	
OSE/DMEPA (proprietary name)	Reviewer:	Ann Crandall	N
	TL:	Melina Griffis	Y
OSE/DRISK (REMS)	Reviewer:	LaShawn Griffiths	Y
	TL:	Mary Dempsey	Y
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	N
	TL:	Tejashri Purohit-Sheth	N

Other reviewers	Chad Reissig, CSS Lori Love, CSS TL Ginneh Stowe, Peds June Cai, SEALD Endpoints	Y Y Y Y
Other attendees		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: July 15, 2010 <input type="checkbox"/> NO <input type="checkbox"/> To be determined <p>Reason:</p>

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments: N/A</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Eric Colman, M.D.; Deputy Director of DMEP 21st Century Review Milestones (see attached) (optional): Comments: 21 st Century Review procedures will be followed	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
X	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
N/A	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
N/A	BLA/BLA supplements: If filed, send 60-day filing letter
N/A	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
X sent	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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

/s/

PATRICIA J MADARA
04/12/2010