# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22580Orig1s000**

# CHEMISTRY REVIEW(S)

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

| | | | |
|---|---|---|---|
| **lication:** | NDA 22580/000 | **Action Goal:** | |
| **mp Date:** | 28-DEC-2009 | **District Goal:** | 17-FEB-2012 |
| **julatory:** | 17-JUL-2012 | | |
| **ıll** | VIVUS | **Brand Name:** | QNEXA (phentermine IR + topiramate modif |
| | 1172 CASTRO ST | **Estab. Name:** | |
| | MOUNTAIN VIEW, CA 94040 | **Generic Name:** | VI-0521 |
| **ırity:** | 4 | **Product Number; Dosage Form; Ingredient; Strengths** | |
| **. Code:** | 510 | 001; CAPSULE; PHENTERMINE; 3.75MG<br>001; CAPSULE; TOPIRAMATE; 23MG<br>002; CAPSULE; PHENTERMINE; 7.5MG<br>002; CAPSULE; TOPIRAMATE; 46MG<br>003; CAPSULE; PHENTERMINE; 11.25MG<br>003; CAPSULE; TOPIRAMATE; 69MG<br>004; CAPSULE; PHENTERMINE; 15MG<br>004; CAPSULE; TOPIRAMATE; 92MG | |

**ılication Comment:** THE CONTACT PERSON FOR THE APPLICATION IS PETER TAM, PHONE: 650-934-5200, EMAIL TAM@VIVUS.COM (on 31-DEC-2009 by D. HENRY () 3017964227)

(b) (4) EER WAS RESUBMITTED DUE TO OUTDATED COMPLIANCE INFORMATION AND EXTENDED REVIEW CYCLE. (on 17-JAN-2012 by M. STOCK (HFD-320) 3017964753)

THE DRUG PRODUCT IS A (b) (4) GELATIN CAPSULE CONTAINING THE ACTIVE INGREDIENTS PHENTERMINE HYDROCHLORIDE AND TOPIRAMATE
AS FORMULATIONS OF PHEN BEADS AND TPM BEADS. (b) (4) GELATIN
CAPSULES ARE FILLED WITH PHEN BEADS AND TPM BEADS IN APPROPRIATE AMOUNTS TO ACHIEVE DESIRED DOSES OF PHENTERMINE AND TOPIRAMATE. (on 04-JAN-2010 by D. HENRY () 3017964227)

THE GOAL DATE FOR THIS APPLICATION IS 10/28/2010. (on 04-JAN-2010 by D. HENRY () 3017964227)

THIS IS A 505(B)(2) APPLCATION WITH TWO DRUG SUBSTANCES. THE REFERENCE LISTED DRUGS ARE:
ADIPEX-P (PHENTERMINE HYDROCHLORIDE)
TEVA PHARMACEUTICALS, USA
NDA 85-128
NDA 88-023
IONAMIN (PHENTERMINE RESIN)
UCB, INC. (ORIGINAL SPONSOR)
NDA 11-613
TOPAMAX® (TOPIRAMATE)
ORTHO-MCNEIL JANSSEN PHARMACEUTICALS, INC.
NDA 20-505
NDA 20-844
(on 31-DEC-2009 by D. HENRY () 3017964227)

| | | | |
|---|---|---|---|
| **\ Contacts:** | D. HENRY | Project Manager | 3017964227 |
| | S. TRAN | Team Leader | 3017961764 |

| | | | | | |
|---|---|---|---|---|---|
| **rail Recommendation:** | ACCEPTABLE | on 10-JUL-2012 | by A. INYARD | (HFD-323) | 3017965363 |
| | PENDING | on 10-JUL-2012 | by EES_PROD | | |
| | PENDING | on 17-JAN-2012 | by EES_PROD | | |
| | ACCEPTABLE | on 05-OCT-2010 | by A. INYARD | (HFD-323) | 3017965363 |

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

ablishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

F No: (b) (4) AADA:

ponsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

ablishment nment: MANUFACTURE PACKAGE AND TEST TOPIRAMATE (on 31-DEC-2009 by D. HENRY () 3017964227)

file: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

| stone Name / Comment | Milestone Date | Request Type | Planned Completion | Decision / Reason | Creator |
|---|---|---|---|---|---|
| MITTED TO OC | 05-JAN-2010 | | | | HENRYD |
| RECOMMENDATION | 05-JAN-2010 | | | ACCEPTABLE<br>BASED ON PROFILE | STOCKM |
| MITTED TO OC | 17-JAN-2012 | | | | STOCKM |
| MITTED TO DO<br>SURVEILLANCE COVERAGE ONLY | (b) (4) | GMP Inspection | | | STOCKM |
| IGNED INSPECTION TO IB<br>SURVEILLANCE COVERAGE ONLY | (b) (4) | GMP Inspection | | | STOCKM |
| PECTION PERFORMED<br>See EIR. | (b) (4) | | | | RORY.GEYER |
| DER REVIEW | 31-MAY-2012 | | | | STOCKM |
| RECOMMENDATION | 10-JUL-2012 | | | ACCEPTABLE<br>BASED ON FILE REVIEW | PHILPYE |
| RECOMMENDATION | 10-JUL-2012 | | | ACCEPTABLE<br>DISTRICT RECOMMENDATION | INYARDA |

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

ablishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

AADA:

ponsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

ablishment nment: MANUFACTURE AND TESTS PHENTERMINE HYDROCHLORIDE (on 31-DEC-2009 by D. HENRY () 3017964227)

file: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

| stone Name | Milestone Date | Request Type | Planned Completion | Decision | Creator |
|---|---|---|---|---|---|
| Comment | | | | Reason | |
| MITTED TO OC | 05-JAN-2010 | | | | HENRYD |
| MITTED TO DO | (b) (4) | GMP Inspection | | | STOCKM |
| IGNED INSPECTION TO IB | | GMP Inspection | | | JOHNSONE |
| RECOMMENDATION | 30-SEP-2010 | | | ACCEPTABLE | STOCKM |
| | | | | BASED ON FILE REVIEW | |
| RECOMMENDATION | 05-OCT-2010 | | | ACCEPTABLE | INYARDA |
| | | | | DISTRICT RECOMMENDATION | |

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

| | | | |
|---|---|---|---|
| **lication:** | NDA 22580/000 | **Action Goal:** | |
| **mp Date:** | 28-DEC-2009 | **District Goal:** | 29-AUG-2010 |
| **julatory:** | 28-OCT-2010 | | |
| **l** | VIVUS | **Brand Name:** | |
| | 1172 CASTRO ST | **Estab. Name:** | |
| | MOUNTAIN VIEW, CA 94040 | **Generic Name:** | VI-0521 |
| **rity:** | 4 | **Product Number; Dosage Form; Ingredient; Strengths** | |
| **. Code:** | 510 | 001; CAPSULE; PHENTERMINE; 3.75MG<br>001; CAPSULE; TOPIRAMATE; 23MG<br>002; CAPSULE; PHENTERMINE; 7.5MG<br>002; CAPSULE; TOPIRAMATE; 46MG<br>003; CAPSULE; PHENTERMINE; 11.25MG<br>003; CAPSULE; TOPIRAMATE; 69MG<br>004; CAPSULE; PHENTERMINE; 15MG<br>004; CAPSULE; TOPIRAMATE; 92MG | | |

**lication Comment:** THE CONTACT PERSON FOR THE APPLICATION IS PETER TAM, PHONE: 650-934-5200, EMAIL TAM@VIVUS.COM (on 31-DEC-2009 by D. HENRY () 301-796-4227)

THIS IS A 505(B)(2) APPLCATION WITH TWO DRUG SUBSTANCES. THE REFERENCE LISTED DRUGS ARE:
ADIPEX-P (PHENTERMINE HYDROCHLORIDE)
TEVA PHARMACEUTICALS, USA
NDA 85-128
NDA 88-023
IONAMIN (PHENTERMINE RESIN)
UCB, INC. (ORIGINAL SPONSOR)
NDA 11-613
TOPAMAX® (TOPIRAMATE)
ORTHO-MCNEIL JANSSEN PHARMACEUTICALS, INC.
NDA 20-505
NDA 20-844
(on 31-DEC-2009 by D. HENRY () 301-796-4227)

THE DRUG PRODUCT IS A (b) (4) GELATIN CAPSULE CONTAINING THE ACTIVE INGREDIENTS PHENTERMINE HYDROCHLORIDE AND TOPIRAMATE
AS FORMULATIONS OF PHEN BEADS AND TPM BEADS. (b) (4) GELATIN
CAPSULES ARE FILLED WITH PHEN BEADS AND TPM BEADS IN APPROPRIATE AMOUNTS TO ACHIEVE DESIRED DOSES OF PHENTERMINE AND TOPIRAMATE. (on 04-JAN-2010 by D. HENRY () 301-796-4227)

THE GOAL DATE FOR THIS APPLICATION IS 10/28/2010. (on 04-JAN-2010 by D. HENRY () 301-796-4227)

| | | | |
|---|---|---|---|
| **\ Contacts:** | D. HENRY | Project Manager | 301-796-4227 |
| | S. TRAN | Team Leader | 301-796-1764 |

**rall Recommendation:** ACCEPTABLE on 05-OCT-2010 by A. INYARD ()

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

**ablishment:** **CFN:** 1055327 **FEI:** 1000110912

CATALENT PHARMA SOLUTIONS LLC

160 N PHARMA DRIVE
MORRISVILLE, NC 27560

**F No:** **AADA:**

**ponsibilities:** FINISHED DOSAGE STABILITY TESTER

**ab. Comment:**

**file:** CONTROL TESTING LABORATORY **OAI Status:** NONE

| stone Name | Milestone Date | Request Type | Planned Completion | Decision | Creator |
|---|---|---|---|---|---|
| **Comment** | | | | **Reason** | |
| BMITTED TO OC | 05-JAN-2010 | | | | HENRYD |
| BMITTED TO DO | 05-JAN-2010 | 10-Day Letter | | | STOCKM |
| RECOMMENDATION | 08-MAR-2010 | | | ACCEPTABLE | JCHANCEY |
| EI CONDUCTED 11/16-18/09 DID NOT REVEAL ANY SIGNIFICANT DEFICIENCIES IN THE FIRM'S LABORATORY OR QUALITY SYSTEMS. NO FDA-483 WAS GIVEN TO THE FIRM AT THE CONCLUSION OF THE INSPECTION.<br><br>NEITHER OF THE PREVIOUS INSPECTIONS THAT WERE CONDUCTED 5/7-9/07 AND 6/19-21/06 RESULTED IN THE ISSUANCE OF A FDA-483 AND BOTH WERE CLASSIFIED AS NAI.<br><br>THE DISTRICT IS RECOMMENDING THAT THIS APPLICATION BE APPROVED BASED UPON THE THE FACILITY'S INSPECTIONAL HISTORY. | | | | BASED ON FILE REVIEW | |
| RECOMMENDATION | 08-MAR-2010 | | | ACCEPTABLE | INYARDA |
| | | | | DISTRICT RECOMMENDATION | |

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

**ablishment:** **CFN:** 1528607 **FEI:** 1000122400

CATALENT PHARMA SOLUTIONS LLC

1100 ENTERPRISE DR
WINCHESTER, KY 403919668

**AADA:**

**po...sibilities:** FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

**ab. Comment:** (b) (4)

(b) (4)

(b) (4) ALSO PERFORMS STABILITY TESTING (on 31-DEC-2009 by D. HENRY () 301-796-4227)

**file:** CAPSULES, PROMPT RELEASE **OAI Status:** NONE

| stone Name | Milestone Date | Request Type | Planned Completion | Decision | Creator |
|---|---|---|---|---|---|
| **Comment** | | | | **Reason** | |
| SMITTED TO OC | 05-JAN-2010 | | | | HENRYD |
| SMITTED TO DO | 05-JAN-2010 | 10-Day Letter | | | STOCKM |
| RECOMMENDATION | 08-MAR-2010 | | | ACCEPTABLE | KCULVER |
| GMP ENDING 12/9/08 WAS VAI. | PROFILE ACCEPTABLE. | | | BASED ON FILE REVIEW | |
| RECOMMENDATION | 08-MAR-2010 | | | ACCEPTABLE | INYARDA |
| | | | | DISTRICT RECOMMENDATION | |

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

**ablishment:** **CFN:** 2530802 **FEI:** 1000522077

CATALENT PHARMA SOLUTIONS LLC

3001 RED LION RD
PHILADELPHIA, PA 19114

**F No:** **AADA:**

**ponsibilities:** FINISHED DOSAGE PACKAGER

**ab. Comment:**

**file:** CAPSULES, PROMPT RELEASE **OAI Status:** NONE

| estone Name | Milestone Date | Request Type | Planned Completion | Decision | Creator |
|---|---|---|---|---|---|
| Comment | | | | Reason | |
| BMITTED TO OC | 05-JAN-2010 | | | | HENRYD |
| RECOMMENDATION | 05-JAN-2010 | | | ACCEPTABLE | STOCKM |
| | | | | BASED ON PROFILE | |

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

**ablishment:** **CFN:** 2249948 **FEI:** 3003563645

CATALENT PHARMA SOLUTIONS, LLC

14 SCHOOLHOUSE RD
SOMERSET, NJ 08873

**AADA:**

**po...ilities:** FINISHED DOSAGE STABILITY TESTER

**ab. Comment:**

**file:** CONTROL TESTING LABORATORY **OAI Status:** NONE

| stone Name | Milestone Date | Request Type | Planned Completion | Decision | Creator |
|---|---|---|---|---|---|
| Comment | | | | Reason | |
| BMITTED TO OC | 05-JAN-2010 | | | | HENRYD |
| RECOMMENDATION | 05-JAN-2010 | | | ACCEPTABLE BASED ON PROFILE | STOCKM |

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

ablishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

F No: AADA:

ponsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE RELEASE TESTER

ab. Comment: MANUFACTURE PACKAGE AND TEST TOPIRAMATE (on 31-DEC-2009 by D. HENRY () 301-796-4227)

file: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

| estone Name | Milestone Date | Request Type | Planned Completion | Decision | Creator |
|---|---|---|---|---|---|
| **Comment** | | | | **Reason** | |
| BMITTED TO OC | 05-JAN-2010 | | | | HENRYD |
| RECOMMENDATION | 05-JAN-2010 | | | ACCEPTABLE BASED ON PROFILE | STOCKM |

# ESTABLISHMENT EVALUATION REQUEST
# DETAIL REPORT

**ablishment:** **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

**AADA:**

**ponsibilities:** DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

**ab. Comment:** MANUFACTURE AND TESTS PHENTERMINE HYDROCHLORIDE (on 31-DEC-2009 by D. HENRY () 301-796-4227)

**file:** NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

| stone Name | Milestone Date | Request Type | Planned Completion | Decision | Creator |
|---|---|---|---|---|---|
| Comment | | | | Reason | |
| BMITTED TO OC | 05-JAN-2010 | | | | HENRYD |
| BMITTED TO DO | (b) (4) | GMP Inspection | | | STOCKM |
| SIGNED INSPECTION TO IB | | GMP Inspection | | | JOHNSONE |
| RECOMMENDATION | 30-SEP-2010 | | | ACCEPTABLE<br>BASED ON FILE REVIEW | STOCKM |
| RECOMMENDATION | 05-OCT-2010 | | | ACCEPTABLE<br>DISTRICT RECOMMENDATION | INYARDA |

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

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/s/

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MARY GRACE LUBAO
07/26/2012

**MEMORANDUM**

**Date:** 12 Mar 2012
**From:** Joseph Leginus, Review Chemist, Branch VII/DPA III/ONDQA
**To:** NDA 22-580, Qnexa® (phentermine/topiramate) Extended-Release Capsule
**Subject:** Container Closure

Background:

- The Applicant (VIVUS) plans to market a new 14-count container bottle for the 3.75 mg/23 mg PHEN/TPM (phentermine/topiramate) Capsule dosage strength [redacted] (b) (4)
- The 14-count container closure system proposed for PHEN/TPM Capsules for the 3.75 mg/23 mg dosage strength is a [redacted] (b) (4) version of the current 30-count container closure system. All materials of product contact are identical.
- The 30-count presentation uses a 60 cc HDPE bottle [redacted] (b) (4) whereas the 14-count presentation uses a 30 cc HDPE bottle [redacted] (b) (4) The bottle seal and cap are identical between the two presentations. Both bottles meet the specifications for a "tight container" when tested in accordance with USP <671>.
- The post-approval stability commitment will be extended to include stability testing of the first three lots of commercial drug product packaged in the 14-count container-closure system.

Conclusions:

- The addition of a 14-count 30 cc HDPE bottle for the 3.75 mg/23 mg PHEN/TPM dosage strength is acceptable. This is based on acceptable stability data previously provided on the similar 30 count-presentation of PHEN/TPM Capsules for the 3.75 mg/23 mg dosage strength in 60 cc HDPE bottles,
- As concluded previously (see Memorandum of 11/08/2011), a shelf-life of 24 months is granted for Qnexa® (phentermine/topiramate) Extended Release Capsules of all four dosage strengths packaged in bottles when stored at the recommended storage condition of 25°C/60% RH.
- The CMC recommendation of Approval continues.

Joseph Leginus, PhD
Review Chemist

Su Tran, Ph.D.
Division III, ONDQA
(Acting for Branch Chief, Branch VII)

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/s/

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JOSEPH LEGINUS
03/12/2012

SUONG T TRAN
03/12/2012

**MEMORANDUM**

**Date:** 8 Oct 2011
**From:** Joseph Leginus, Review Chemist, Branch VII/DPA III/ONDQA
**To:** NDA 22-580, QNEXA® (phentermine/topiramate) Extended Release Capsule
**Subject:** Expiration Dating Period (Expiry)

Background:

- In Chemistry Review #2 (10 Sep 2010) for NDA 22-580, a shelf-life of 12 months was granted for QNEXA capsules when maintained at the recommended storage condition of 25°C/60% RH. This determination was based on the available acceptable stability data (8 months of real-time and 6 months of an intermediate condition) submitted with the original NDA on 28-Dec-2009.
- On 17 Oct 2011, the applicant submitted a Complete Response Submission that included formal responses to the Division's Complete Response Letter of 28 Oct 2010. Also included in this resubmission were stability updates for the drug product.

Stability Update:

- Of the four drug product strengths, only the highest (PHEN/TPM 15/92 mg) and lowest strengths (PHEN/TPM 3.75/23 mg) were evaluated for stability based on a bracketing strategy. The stabilities of the intermediate strengths (PHEN/TPM 7.5/46 mg and PHEN/TPM 11.25/69 mg) will be bracketed by the highest and lowest strengths.
- 18 months of real time (25°C/60% RH) stability data and 12 months of stability data at an intermediate condition (30°C/65% RH) have been provided for the drug product registration batches packaged in (b) (4) b) bottles. (As previously stated to the applicant at the 22 July 2009 pre-NDA meeting, the registration batches would be considered the primary stability batches for the purpose of determining an expiration dating period for the product). The updated stability data indicate acceptable stability of the drug product in (b) (4) (b) (4) bottles for the length of these studies.

Conclusion:

- The applicant has provided 18 months of acceptable real time (25°C/60% RH) and 12 months of acceptable stability data at an intermediate condition (30°C/65% RH) for the registration drug product batches packaged in (b) (4) bottles. Based on these data, and as detailed in ICH Q1E Evaluation of Stability Data, a shelf-life of 24 months is granted for QNEXA® (phentermine/topiramate) Extended Release Capsules of all four dosage strengths packaged in (b) (4) bottles when stored at the recommended storage condition of 25°C/60% RH.

Joseph Leginus, PhD
Review Chemist

Ali Al-Hakim, Ph.D.
Branch VII, Chief, ONDQA

---

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

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/s/

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JOSEPH M LEGINUS
11/08/2011

ALI H AL HAKIM
11/08/2011

# NDA 22-580

## QNEXA®
## (phentermine/topiramate)
## Extended Release Capsule

## VIVUS, Inc.

**Joseph Leginus, PhD**
**Division of Pre-Marketing Assessment III, Branch VII, ONDQA**

## For the Division of
## Metabolism and Endocrinology Products

## CHEMISTRY REVIEW #2

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# Chemistry Review Data Sheet

1. NDA 22-580

2. REVIEW #: 2

3. REVIEW DATE: 10-Sept-2010

4. REVIEWER: Joseph Leginus, PhD

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original NDA | 28-Dec-2009 |
| Amendment | 19-Mar-2010 |
| Amendment | 07-May-2010 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment | 24-Jun-2010 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | VIVUS, Inc. |
| Address: | 1172 Castro St., Mountain View, CA 94040 |
| Representative: | Peter Tam, President, VIVUS, Inc. |
| Telephone: | 650-934-5309 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: QNEXA®
b) Non-Proprietary Name (USAN): Phentermine/Topiramate
c) Code Name/# (ONDC only): VI-0521; PHEN/TPM Capsules
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4 (New Combination)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.

10. PHARMACOL. CATEGORY:
Combination centrally acting appetite suppressant.

11. DOSAGE FORM: Extended Release Capsule

12. STRENGTH/POTENCY:
QNEXA capsules are manufactured in four strengths (phentermine free base/topiramate): 3.75/23 mg, 7.5/46 mg, 11.25/69 mg and 15/92 mg.[1]

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

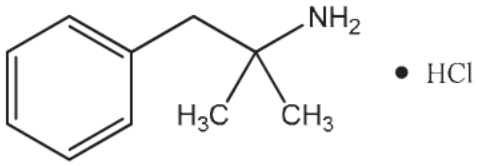
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

A. Phentermine Hydrochloride
Chemical Names: i) Benzeneethanamine-α,α-dimethyl hydrochloride
ii) α,α-Dimethylphenethylamine hydrochloride

Structural Formula:




Molecular Formula: $C_{10}H_{15}N \bullet HCl$

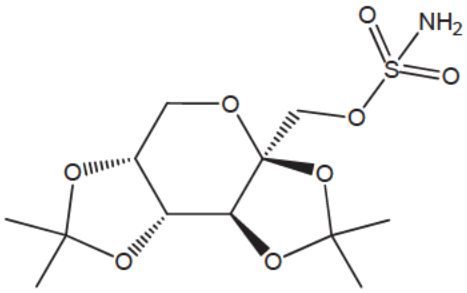
Molecular Weight: 185.69 (hydrochloride salt)
149.23 (free base)

[1] Reference to the dosage strength should be indicated as "x mg/y mg" instead of "x/y mg". However, for the purposes of this review, dosage strengths will be indicated as originally presented by the applicant in the NDA. See Chemistry Review #1 (8-Jun-2010), Section II. Review of Common Technical Document-Quality (Ctd-Q) Module 1, A. Labeling & Package Insert for recommended changes to the label for dosage strengths.

B. Topiramate

Chemical Names: i) 2,3:4,5-Bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate
ii) β-D-fructopyranose, 2,3:4,5-bis-O-(1-methylethylidene)-sulfamate
iii) 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate

Structural Formula:



Molecular Formula: $C_{12}H_{21}NO_8S$

Molecular Weight: 336.36

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | Type | Holder | Item Referenced | Code[1] | Status[2] | Date Review Completed | Comments |
|---|---|---|---|---|---|---|---|
| (b) (4) | II | | (b) (4) | 1 | Adequate | 12-Dec-2006 | Reviewed by D. Maldonado |
| | II | | | 1 | Adequate | 23-Dec-2009 | Reviewed by L. Hussain |
| | IV | | | 1 | Adequate | 22-Jan-2003 | Reviewed by G. Lunn |
| | III | | | 1 | Adequate | 17-Jul-2007 | Reviewed by D. Klein |
| | III | | | 1 | Adequate | 22-Sep-2004 | Reviewed by S. De |
| | III | | | 1 | Adequate | 05-Jul-2000 | Reviewed by D. Shad |
| | III | | | 1 | Adequate | 24-Sep-2007 | Reviewed by C. Bertha |
| | III | | | 1 | Adequate | 09-Mar-2009 | Reviewed by B. Kurtyka |
| | III | | | 1 | Adequate | 07-Dec-2009 | Reviewed by Y. Tang |
| | III | | | 1 | Adequate | 16-Jul-2004 | Reviewed by L. Hsieh |
| | III | | | 1 | Adequate | 20-Nov-2007 | Reviewed by Y. Sun |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| IND | 68,651 | Phentermine/Topiramate |
| IND | (b) (6) | Phentermine/Topiramate fixed dose combination |
| NDA | 20-505 | Topiramate (Topamax) |

## 18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Pending. All facilities are Acceptable except the drug substance (phentermine hydrochloride) manufacturer (b) (4) Inspection assigned to Investigations Branch. | (b) (4) | N/A |
| Biopharmaceutics | Acceptable. Evaluation of dissolution data provided. | 10-Sept-2010 | Albert Chen |
| Methods Validation | Validation may be requested of FDA labs after test methods are finalized. | N/A | N/A |
| EA | Adequate. | 8-Jun-2010 | Joseph Leginus |
| Microbiology | Not required as per ICH Q6A. The solid dosage form has been shown during development not to support microbial viability or growth. | N/A | N/A |

## 19. ORDER OF REVIEW: N/A

# The Chemistry Review for NDA 22-580

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

NDA 22-580 is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

Note: The overall recommendation from the Office of Compliance for GMP inspections is still outstanding; the CMC recommendation does not incorporate any potential facility inspection issues.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

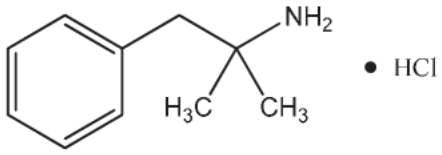
Not applicable.

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCES

**Phentermine Hydrochloride**
Phentermine hydrochloride (contraction of "**phen**yl-**ter**tiary-butyla**mine**") was approved in 1959 (NDA 11-613) as an appetite suppressant and is currently approved as a generic in several dosage forms including an immediate release capsule (ANDA 088023). It is an amphetamine chemically designated as α,α-dimethyl phenethylamine hydrochloride having the structure shown below.

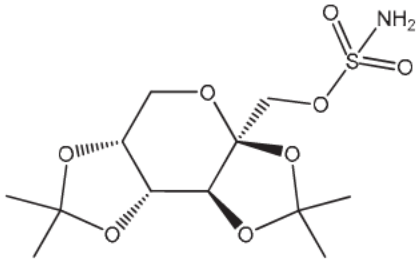



Phentermine hydrochloride is a white, odorless, hygroscopic, crystalline powder that is soluble in water and alcohols, slightly soluble in chloroform and insoluble in ether. Specifications are based on the USP monograph. In addition, the drug substance is tested for (b) (4) Retest for the drug substance is (b) (4) Information for phentermine hydrochloride is provided in the (b) (4) Type II DMF (b) (4) and is incorporated by reference herein. A copy of the letter of authorization

to reference DMF (b) (4) has been provided. DMF (b) (4) was reviewed on 12-Dec-2006 and found to be adequate.

**Topiramate**

Topiramate was approved in 1996 (NDA 20-505, Topamax®) as an anticonvulsant and was approved as a generic in 2006. Topiramate is a sulfamate-substituted monosaccharide, related to fructose, having the following structure:



Topiramate is a white crystalline compound with a bitter taste. It is slightly soluble in water and most soluble in aqueous solutions at pH 9 – 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The specifications for topiramate drug substance conform to the USP Topiramate monograph and also include appearance, (b) (4) melting range and particle size.

Information for topiramate is provided in the (b) (4) Type II DMF (b) (4) and is incorporated by reference herein. A copy of the letter of authorization to reference DMF (b) (4) has been provided. DMF (b) (4) was reviewed on 23-Dec-2009 and found to be adequate.

DRUG PRODUCT

Qnexa® extended release oral capsules are a combination product comprised of immediate-release phentermine hydrochloride beads (PHEN) and extended-release topiramate beads (TPM). PHEN Beads are formulated for (b) (4)

Both bead types are filled into a (b) (4) gelatin capsule as generally illustrated below. (b) (4)

(b) (4)

Qnexa capsules are manufactured in four dosage strengths (PHEN/TPM) containing the two drug substances (b) (4) The quantitative composition is indicated as milligrams by weight of phentermine (calculated as the free base) and topiramate as follows:

PHEN/TPM 3.75/23 mg (low dose)
PHEN/TPM 7.5/46 mg (mid dose)
PHEN/TPM 11.25/69 mg (three-quarter dose)
PHEN/TPM 15/92 mg (full dose)

Although the same capsule size (Size 0) is used, each dosage strength is differentiated by a unique combination of capsule colors and printing.

PHEN Beads are manufactured by (b) (4)

(b) (4)

TPM Beads are manufactured by (b) (4)

(b) (4)

The proposed release specifications include phentermine and topiramate identity (HPLC), assay (HPLC), related substances (HPLC), content uniformity and dissolution;

appearance, impurities (b) (4) and microbial limits. All non-compendial regulatory methods have been validated.

Qnexa will be packaged in (b) (4) bottle – at four dosage strengths. (b) (4)

(b) (4)

Bottled product: The four strengths of Qnexa capsules are separately packaged in (b) (4), foil-sealed, high density polyethylene bottles containing 30 capsules (b) (4).

As stated to the applicant (at the 22 July 2009 pre-NDA meeting), the registration drug product batches would be considered the primary stability batches for the purpose of determining an expiration dating period for the product. Of the four strengths, only the highest (PHEN/TPM 15/92 mg) and lowest strengths (PHEN/TPM 3.75/23 mg) were tested for stability based on an acceptable bracketing strategy. The applicant has provided only 8 months of acceptable real time (25°C/60% RH) stability data for the registration batches packaged in (b) (4) bottles. Additional acceptable stability data was generated at an intermediate condition (30°C/65% RH) through six months; however, significant changes to the drug product were observed prior to six months at the accelerated condition (40°C/75% RH) for each strength capsule in (b) (4) bottles. Based on these data, and as detailed in ICH Q1E Evaluation of Stability Data, a shelf-life of 12 months is granted for Qnexa capsules when maintained at the recommended storage condition of 25°C/60% RH.

Vivus, Inc. has submitted an acceptable environmental assessment for Qnexa (b) (4) (b) (4) pursuant to 21 CFR part 25 showing that concentrations of phentermine hydrochloride and topiramate at the point of entry into the aquatic environment are below the threshold value of 1 ppb. As a result, the impact from estimated usage of Qnexa capsules on the environment would be negligible.

**B. Description of How the Drug Product is Intended to be Used**

Qnexa extended release capsule is indicated for the treatment of obesity, including weight loss and maintenance of weight loss, in conjunction with diet and exercise. The recommended dose of Qnexa is 7.5/46 mg (phentermine/topiramate), taken once daily in the morning with or without food. Treatment should be initiated using a dose titration starting with the 3.75/23 mg dose for 7 to 14 days followed by the daily dose of 7.5/46 mg. If weight loss goals have not been achieved after 3 - 4 months of treatment, titration from the dose level of 7.5/46 mg to the 15/92 mg dose may be considered. The 15/92 mg dose should be achieved by increasing the daily dose from 7.5/46 mg to 11.25/69 mg for 7 to 14 days prior to increasing the daily dose to 15/92 mg. The drug product will be labeled for long term storage at controlled room temperature (15°C - 25°C; 59°F – 77°F).

**C. Basis for Approvability or Not-Approval Recommendation**

All items in the List of Deficiencies from Chemistry Review #1 have been satisfactorily addressed in the 24-Jun-2010 amendment to the original NDA. See Chemistry Assessment section below for details.

This is a 505(b)(2) application providing for a new extended release combination product (oral capsule). The reference listed drugs (RLD) are Adipex-P (phentermine hydrochloride; ANDA 085128, 088023) and Topamax® (topiramate; NDA 20-505). The associated IND is 68,651 which was received on 11/19/2003. A pre-NDA meeting was held on 7/22/2009.

Drug substance phentermine hydrochloride will be manufactured for commercial use by (b) (4) with most of the CMC parameters provided in the Type II DMF No. (b) (4) A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be adequate.

Drug substance topiramate will be manufactured for commercial use by (b) (4) (b) (4) with most of the CMC parameters provided in the Type II DMF No. (b) (4) A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be adequate.

The drug product, Qnexa® (phentermine/topiramate) Extended Release Capsule will be manufactured by Catalent Pharma Solutions located in Kentucky, USA as a combination product comprised of phentermine beads (phentermine hydrochloride, (b) (4) and topiramate beads (topiramate, (b) (4) in a size 0 hard gelatin capsule. All excipients comply with corresponding USP and NF monographs. All capsule components have compendial references (gelatin, titanium dioxide), are approved food additives (FD&C colorants) or are food grade quality (printing ink).

A 24 months expiry period for the drug product was requested, however, due to limited stability data (8 months of real time stability provided for the registration batches), an expiry of 12 months will be granted for each of the four dosage strengths of Qnexa in (b) (4) bottles when stored at the recommended storage condition of 25°C.

An evaluation of Acceptable was provided from the Biopharmaceutics Reviewer for the dissolution data (see review of Tien-Mien Chen; 09/10/10).

The overall recommendation from the Office of Compliance for GMP inspections is still outstanding; the CMC recommendation does not incorporate any potential facility inspection issues.

## III. Administrative

**A. Reviewer's Signature:** in DAARTS
**B. Endorsement Block:** in DAARTS
**C. CC Block:** in DAARTS

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

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/s/

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JOSEPH M LEGINUS
09/10/2010

ALI H AL HAKIM
09/10/2010

# ONDQA BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA#**: | 22-580 (N-000) |
| **Submission Date:** | 08/27/10 and 09/08/10 (Telecon) |
| **Brand Name**: | Qnexa |
| **Generic Name**: | Phentermine/Topiramate (Phen/Tpm) |
| **Formulation:** | Fixed Dose Combination (FDC) Oral Capsules |
| **Strength**: | 15/92 mg, 11.25/69 mg, 7.5/46 mg, and 3.75/23 mg |
| **Sponsor**: | Vivus |
| **Type of submission:** | Amendment |
| **Reviewer**: | Tien-Mien Chen, Ph.D. |

**SUMMARY**

NDA 22-580 for Qnexa (Phen/Tpm) FDC oral capsules was reviewed on 07/19/10. The Agency sent a general advice letter on 07/23/10 for its proposed revisions to the dissolution specifications for both Phen and Tpm. On 08/27/10, the sponsor responded to the above advice letter. Therefore, the 08/27/10 response is reviewed here.

The Agency's proposal in the 07/23/10 advice letter is summarized as shown below and followed by the 08/27/10 sponsor's rationale and/or counter-proposal. Please see the sponsor's responses in Appendix 1 for details.

1. For Phen: The Agency proposed revisions to the dissolution specification are as follows.

   To change From: **Q=** (b) (4) **in 30 min**
   To: **Q=** (b) (4) **in 15 min**

   VIVUS does not agree with the FDA-proposed specification for Phen dissolution. The sponsor would like to keep the originally proposed specifications, i.e., **Q=** (b) (4) **in 30 min** for the currently available stability and clinical batches had only one sampling timepoint at 30 min.

2. For Tpm: The Agency's proposed dissolution specifications are shown below.

   Proposed specifications: (b) (4) **at 0.5 hr**
   (b) (4) **at 2 hr**
   **NLT** (b) (4) **at 6 hr**

   VIVUS does not agree with the FDA-proposed specification for Tpm dissolution at 0.5 hr and 2 hr, but accepted the FDA-proposed specification for Tpm dissolution at the 6-hr timepoint as shown below.

**Table 1. Proposed Tpm Dissolution Specifications**

| Timepoint (h) | Proposed Specifications - FDA | Proposed Specifications - VIVUS |
|---|---|---|
| 0.5 | (b) (4) | |
| 2 | | |
| 6 | NLT (b) (4) | NLT (b) (4) |

On 09/08/10, a Telecom was held between the Agency and the sponsor to discuss and resolve the dissolution specification issues. It was concluded and agreed upon at the end of the meeting that

- For Phen, since the stability and clinical batches had only one sampling timepoint at 30 min, the sponsor's proposal of Q= (b) (4) at 30 min is acceptable.
- For Tpm, the following specifications as recommended by the Agency sustained.

(b) (4) **at 0.5 hr**
**at 2 hr**
**NLT** (b) (4) **at 6 hr**

**RECOMMENDATION**:
From the Biopharmaceutics perspective; 1) The above dissolution specifications for Phen and Tpm agreed upon between the Agency and Vivus at the end of 09/08/10 Teleconference are final, and 2) The acceptance criteria for the finished product will be updated with the final dissolution specifications as shown below.

- For Phen, **Q=** (b) (4) **at 30 min**
- For Tpm, (b) (4) **at 0.5 hr**
  (b) (4) **at 2 hr**
  **NLT** (b) (4) **at 6 hr**

No further comments are to be sent to the sponsor. From the Biopharmaceutics perspective NDA 22-580 QNEXA Capsules is acceptable

09/08/10
Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

09/08/10
Angelica Dorantes, Ph.D. Date
ONDQA Biopharmaceutics Team leader

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

# NDA 22-580 for Qnexa (Phen IR + Tpm ER) Oral Capsules, 15/92 mg, 11.25/69 mg, 7.5/46 mg, and 3.75/23 mg

# Appendix 1

# Sponsor's 08/27/10 Responses to Agency's 07/23/10 Advice Letter

On 08/27/10, the sponsor responded (with their justifications) to 07/23/10 Agency's advice letter for the revisions to the proposed dissolution specifications for both Phen and Tpm. The sponsor proposed as follows.

1. For Phen:

VIVUS does not agree with the FDA-proposed specification for Phentermine dissolution for the following reasons:

a. Phentermine is not a narrow therapeutic index active ingredient, and has a long half-life as demonstrated in the QNEXA clinical studies (see Section 2.5). Batches meeting the Q = (b) (4) in 30-minute specification were used throughout the QNEXA clinical program. A 15-minute dissolution time is not necessary for Phentermine to be effective and safe as demonstrated by the clinical program.

b. QNEXA is a (b) (4) gelatin capsule containing a (b) (4) formulation of the active ingredients Phentermine Hydrochloride and Topiramate as proprietary formulations of PHEN Beads and TPM Beads (see Module 3.2.P.1). (b) (4) the (b) (4) manufacturer, provides a disintegration specification of NMT (b) (4) (b) (4) for the capsule shells in their Certificate of Analysis (see Module 3.2.P.4.1). Setting a Q value of (b) (4) for the release of Phentermine from these capsule shells at the same (b) (4) timepoint is not supported by the specification for the capsule shells and could lead to drug product being rejected unnecessarily.

c. The majority of USP monographs for oral immediate-release capsule drug products with dissolution specifications have acceptance limits specified at the 30-minute timepoint. VIVUS proposed value of Q = (b) (4) in 30 minutes is consistent with industry practice for immediate release drug products provided as capsules.

Reviewer's Comment:
The sponsor's counter-proposal is acceptable, since the stability and clinical batches had only one sampling timepoint at 30 min.

2. For Tpm:

FDA and VIVUS proposed dissolution specifications for topiramate are shown in Table 1 below:

**Table 1. Proposed Tpm Dissolution Specifications**

| Timepoint (h) | Proposed Specifications - FDA | Proposed Specifications - VIVUS |
|---|---|---|
| 0.5 | (b) (4) | |
| 2 | | |
| 6 | NLT (b) (4) | NLT (b) (4) |

VIVUS accepts the FDA-proposed specification for Topiramate dissolution at the 6-hr timepoint. VIVUS does not agree with the FDA-proposed specification for Topiramate dissolution at 0.5 hr and 2 hr for the following reasons:

a. Topiramate is not a narrow therapeutic index active ingredient, and has a long half-life as demonstrated in the Qnexa clinical studies (see Module 2.5). Tight dissolution specifications are not required to assure a safe and effective drug product.

b. The 0.5-h timepoint proposed by VIVUS in Table 1 is in place only to ensure that no dose dumping will occur. The 0.5-hr timepoint is on the steepest part of the dissolution curve and therefore is subject to the highest variability in measurement. While VIVUS acknowledges FDA's analysis of the overall mean data, VIVUS, in establishing its proposed specifications, has taken into account individual capsule data in order to address USP <711> requirements. Individual capsule dissolution results range from [redacted] (b) (4) (see Module 3.2.P.5.4). VIVUS' proposed specification for the 0.5-h timepoint is [redacted] (b) (4) and makes allowance for the individual data showing wider variation than the mean. VIVUS contends that these limits are appropriate for a non-narrow therapeutic index drug. Tightening the acceptance limits at the 0.5-hr timepoint could lead to unnecessary and burdensome additional dissolution testing or to rejection of acceptable drug product.

Reviewer's Comment:
The sponsor's counter-proposal is not acceptable. Therefore, the specifications as recommended by the Agency are sustained.

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

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/s/

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TIEN MIEN CHEN
09/10/2010

ANGELICA DORANTES
09/10/2010

# ONDQA BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA#**: | 22-580 (N-000) |
| **Submission Date:** | 12/28/09, 04/21/10, and 07/09/10 |
| **Brand Name**: | Qnexa |
| **Generic Name**: | Phentermine/Topiramate (Phen/Tpm) |
| **Formulation:** | Fixed Dose Combination (FDC) Oral Capsules |
| **Strength**: | 15/92 mg, 11.25/69 mg, 7.5/46 mg, and 3.75/23 mg |
| **Sponsor**: | Vivus |
| **Type of submission:** | Original |
| **Reviewer**: | Tien-Mien Chen, Ph.D. |


**SUMMARY**

Adipex-P has been approved [Phen 37.5 mg immediate release (IR) oral capsules under NDA 88-023 and 37.5 mg IR oral tablet under NDA 85-128]. Topamax has also been approved [Tpm 200 mg, 100 mg, 50 mg, and 25 mg IR oral tablets (NDA 20-505) and 25 mg and 15 mg IR oral capsules (NDA 20-844)].

On 12/28/09, Vivus submitted NDA 22-580 (N-000) for Qnexa (Phen/Tpm FDC oral capsules), a combination of Phen and Tpm containing lower doses of these components. Qnexa is submitted under 505(b)(2) referencing the above monotherapy NDAs. 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.

Phen is manufactured as IR minitablets (beads) and Tpm, as extended release (ER) minitablets (beads). Qnexa (Phen/Tpm FDC capsule) contains a (b) (4)

diagram below.

(b) (4)

The sponsor is seeking approval of 4 dosage strengths, 15/92 mg, 11.25/69 mg, 7.5/46 mg, and 3.75/23 mg oral capsules. These four strengths show the same composition and exhibit dose proportionality.

There is no biowaiver issue since the to-be-marketed formulation (TBM) was either tested clinically (the highest strength) or linked to the clinically tested formulations of the three lower strengths in a bioequivalence (BE) study (No. OB-109). The above BE study is currently under review by the Office of Clinical Pharmacology (OCP).

Per Agency's requests, the sponsor submitted 1). On 04/21/10, the results of an *in vitro* 40% alcohol dose-dumping study for Qnexa capsule and 2) On 07/09/10, the missing dissolution raw and mean data on Tpm. Therefore, the *in vitro* 40% alcohol dose-dumping study results, the missing dissolution data on Tpm, and the proposed dissolution methodology and specifications for Phen and Tpm are reviewed here.

The results of the *in vitro* dose-dumping of 40% alcohol in the dissolution medium (water) showed that 40% alcohol accelerated the release of Tpm from Qnexa capsules and completed the release of Tpm in around 3-4 hrs which is faster than that in water (around 8 hrs). This reviewer consulted Office of Clinical Pharmacology (OCP) regarding the need for an *in vivo* alcohol interaction pharmacokinetic (PK) study. It is concluded by OCP (Dr. Johnny Lau) that

> "Clin Pharm did not request an *in vivo* interaction study between alcohol and phentermine/topiramate since the TOPAMAX label already has caution for coadminstration of alcohol and topiramate (Section 7.3)."

The dissolution methodology for testing Phen and Tpm in Qnexa capsules and the proposed specifications are shown below.

| | |
|---|---|
| **Apparatus**: | 1 (Basket) at 100 rpm |
| **Medium**: | 750 ml deareated deionized water at 37 °C |
| **Sampling**: | For Phen: at 0.5 hr<br>For Tpm: at 0.5, 2, 6 hr |
| **Specifications**: | For Phen: Q= (b) (4) at 0.5 hr |
| | For Tpm: Q= NMT (not more than) (b) (4) at 0.5 hr<br>Q= (b) (4) at 2 hr<br>Q= NLT (not less than) (b) (4) at 6 hr |

The dissolution methodology for Qnexa capsule is acceptable, however, the proposed specifications for Phen and Tpm needed further revisions.

**RECOMMENDATION**

The following comments need to be conveyed to the sponsor and the dissolution specifications for both Phentermine and Topiramate are further revised per Agency's recommendations.

**COMMENTS**: (Need to be sent to the sponsor)

1. The proposed dissolution specification for Phentermine should be revised as follows:

To change From: **Q= (b) (4) in 30 min**
To: **Q= (b) (4) in 15 min**

2. The Agency's proposed dissolution specifications for Topiramate are shown below.

Proposed specifications: **Q= (b) (4) at 0.5 hr**
**Q= (b) (4) at 2 hr**
**Q= NLT (b) (4) at 6 hr**

The above specifications are based on 1) the overall dissolution data submitted on 07/07/10 for 12 registration lots and 15 clinical lots tested and 2) Agency's IVIVC guidance (p.17), under "Setting Specifications Without IVIVC".

The variations (i.e., standard deviation) among the lots are relatively small, therefore, a (b) (4) from the overall means, at 0.5 hr (b) (4) 2 hr (b) (4) and 6 hr (b) (4) was employed for setting the range of release. A (b) (4) width is not justified due to the low variability observed in the dissolution results.

**BACKGROUND**

Adipex-P has been approved [Phen 37.5 mg immediate release (IR) oral capsules under NDA 88-023 and 37.5 mg IR oral tablet under NDA 85-128]. Phen HCL, a synthetic sympathomimetic amine, is an anorectic agent and is indicated as a short-term adjunct to a weight loss regimen based on exercise, behavior modification, and caloric restriction.

Topamax has also been approved [Tpm 200 mg, 100 mg, 50 mg, and 25 mg IR oral tablets (NDA 20-505) and 25 mg and 15 mg IR oral capsules (NDA 20-844)]. Tpm is a neurotherapeutic agent approved for the treatment of seizure disorders at recommended doses of 200–400 mg/day and for migraine headache prophylaxis at recommended doses of 100–200 mg/day. However, it is reported that Tpm monotherapy produces significant weight loss in obese individuals and clinically meaningful improvements in lipids, glycemic control, and blood pressure.

**CURRENT SUBMISSION**

On 12/28/09, Vivus submitted NDA 22-580 (N-000) for Qnexa (Phen/Tpm FDC oral capsules), a combination of Phen and Tpm containing lower doses of these components. Qnexa is submitted under 505(b)(2) referencing the above monotherapy NDAs.

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. VI-0521 is recommended for obese patients (BMI = 30 $kg/m^2$), or overweight patients (BMI = 27 $kg/m^2$) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

The sponsor is seeking approval of 4 dosage strengths, 15/92 mg, 11.25/69 mg, 7.5/46 mg, and 3.75/23 mg oral capsules. These four strengths (b) (4) exhibit dose proportionality.

There is no biowaiver issue since the TBM was either tested clinically (the highest strength) or linked to the clinically tested formulations of the three lower strengths in a bioequivalence (BE) study (No. OB-109). The above BE study is currently under review by the Office of Clinical Pharmacology OCP.

Per OCP request during the pre-NDA meeting and after the fling meeting, the sponsor submitted on 04/21/10, the *in vitro* 40% alcohol dose-dumping study results. On 07/05/10, the Agency also requested 1). The submission of missing/additional dissolution data and 2). Revisions to the proposed specifications for Tpm of Qnexa FDC capsules. The sponsor responded on 07/09/10.

The *in vitro* 40% alcohol dose-dumping study results for Qnexa capsule, the submitted additional dissolution data for Tpm, and the above dissolution methodology and proposed specifications are reviewed here.

**FORMULATION COMPARISONS**

Qnexa (Phen/Tpm FDC capsule) contains a (b) (4) formulation of Phen IR beads and Topiramate ER beads as shown in a schematic diagram (Figure 1 above).

The four strengths of Qnexa (b) (4) exhibit dose proportionality below.

**Table 1. Four Strengths of Qnexa (Phen/Tpm) Capsules**

| Dosage Strength | Phentermine Content (expressed as free base) (mg) | Topiramate Content (mg) | Capsule Color (print ink) |
|---|---|---|---|
| PHEN/TPM 3.75/23 mg | 3.75 | 23 | Purple Body, Purple Cap, (White Print) |
| PHEN/TPM 7.5/46 mg | 7.5 | 46 | Yellow Body (Black Print), Purple Cap (White Print) |
| PHEN/TPM 11.25/69 mg | 11.25 | 69 | Yellow Body, Yellow Cap, (Black Print) |
| PHEN/TPM 15/92 mg | 15 | 92 | White Body, Yellow Cap, (Black Print) |

Phen IR beads are manufactured at (b) (4)

(b) (4)

(b) (4)

Individual or multiple batches of Tpm beads are (b) (4)

The composition of Phen/Tpm FDC capsules are shown below.

**Table 4. The Composition of Phen/Tpm Capsules**

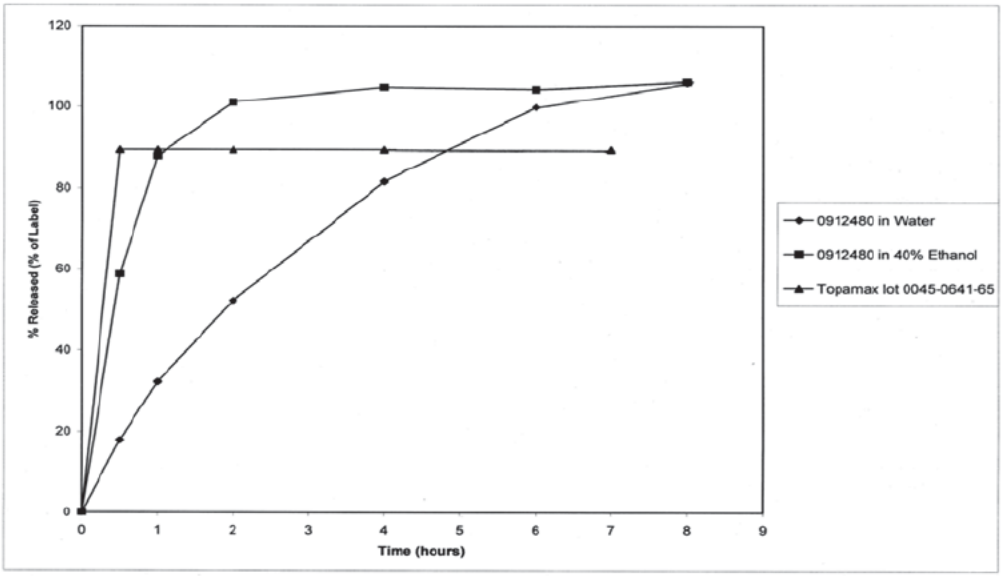
| Component | PHEN/TPM 3.75/23 mg | PHEN/TPM 7.5/46 mg | PHEN/TPM 11.25/69 mg | PHEN/TPM 15/92 mg |
|---|---|---|---|---|
| PHEN | (b) (4) | | | |
| PHEN | | | | |
| TPM | | | | (b) (4) |
| Printed (b) (4) Gelatin Capsule [a] | one | one | one | one |

a. (b) (4) gelatin capsule colors are assigned by dosage strength (See Table 5).

## *IN VITRO* ALCOHOL DOSE-DUMPING STUDY

Per OCP request during the pre-NDA meeting and after the filing meeting of this NDA, the sponsor submitted the results of the *in vitro* 40% alcohol dose-dumping study on Qnexa capsule. The results submitted also included the approved Topamax (Tpm) IR drug product as shown below.

**Figure 2. Topiramate Dissolution Profiles from Registration Batch of Qnexa Capsule 15/92 mg in Water and in 40% Ethanol.**




The results of the *in vitro* dose-dumping of 40% alcohol in the dissolution medium (water) showed that 40% alcohol accelerated the release of Tpm from Qnexa capsule and completed the release of Tpm in 2 hrs which is faster than that in water (around 8 hrs).

Reviewer's Comment:
This reviewer consulted OCP regarding the need for an *in vivo* alcohol interaction PK study. It was concluded by OCP (Dr. Johnny Lau) that

> "The Office of Clinical Pharmacology did not request an *in vivo* interaction study between alcohol and phentermine/topiramate since the TOPAMAX label already has caution for coadminstration of alcohol and topiramate (Section 7.3)."

The sponsor will update and include a similar statement in the Qnexa labeling.

**DISSOLUTION METHOD AND SPECIFICATIONS**
Dissolution methodology for testing Phen and Tpm in Qnexa capsules and the proposed specifications are shown below.

**Apparatus**: 1 (Basket) at 100 rpm
**Medium**: 750 ml deareated deionized water at 37 °C
**Sampling**: For Phen: at 0.5 hr
For Tpm: at 0.5, 2, 6 hr

**Specifications**: For Phen: Q= (b) (4) at 0.5 hr

For Tpm: Q= NMT (b) (4) at 0.5 hr
Q= (b) (4) at 2 hr
Q= NLT (b) (4) at 6 hr

For Phen IR:
The above proposed dissolution apparatus and speed are different from the FDA currently approved dissolution method for Phen IR capsules, i.e., Apparatus II (paddle) with 50 rpm in deareated water at 37 °C. The proposed sampling time point is only at 30 min as the sponsor reported that Phen dissolved rapidly ( (b) (4) dissolved in <30 min).

The typical comparative dissolution profiles for Phen using the proposed dissolution method are shown below.

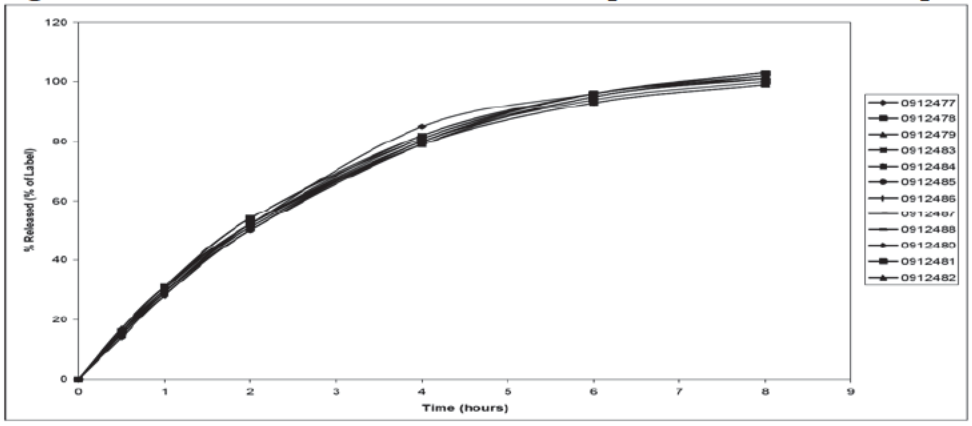
**Figure 3. Mean Dissolution Profiles of Phen Beads in Qnexa Capsules**


**Note**: Per agreement in the 07/22/09 Pre-NDA meeting between the Agency and the applicant, the stability protocol only tested the lowest strength (3.75/23 mg) and the highest strength (15/92 mg) based on a bracketing strategy. The mean dissolution profiles for the other two intermediate strengths (7.5 mg/46 mg and 11.25/69 mg), however, are not located in this submission.

For Tpm ER:
There is no currently FDA approved and/or USP dissolution methodology available. However, the sponsor adopted the same dissolution medium from Phen and proposed sampling time at 0.5, 2, and 6 hours for Tpm.

The typical comparative dissolution profiles for Tpm using the proposed dissolution method are shown below.

**Figure 4. Mean Dissolution Profiles of Tpm Beads in Qnexa Capsules**




1. Registration lot#s 0912477, 0912478, and 0912479 are for 3.75/23 mg FDC capsules.
2. Registration lot#s 0912483, 0912484, and 0912485 are for 7.5/46 mg FDC capsules.
3. Registration lot#s 0912486, 0912487, and 0912488 are for 11.25/69 mg FDC capsules.
4. Registration lot#s 0912480, 0912481, and 0912482 are for 15/92 mg FDC capsules.

Upon request, the sponsor on 07/07/10 submitted 1). Raw and mean dissolution data of the above 12 registration lots plus that of the 15 clinical lots tested and 2). Overall mean dissolution results of all 27 lots as shown below. Please see 07/07/10 response to the Agency's IR dated 07/05/10 in Appendix 1 for details.

**Table 5. Topiramte % Release (of Label Claim) Over Time (n=27 lots)**

| Time (hr) | 0.5 | 1 | 2 | 4 | 6 | 8 |
|---|---|---|---|---|---|---|
| Overall Mean | 18 | 30 | 55 | 81 | 97 | 101 |
| SD | 2.5 | 1.1 | 4.2 | 1.8 | 3.3 | 1.4 |
| Minimum | (b) (4) | | | | | |
| Maximum | | | | | | |

SD: standard deviation.

Based on the above overall mean values at the proposed time points 0.5, 2, and 6 hrs, the sponsor further proposed the release specifications for Tpm as follows.

**Specifications**: For Tpm: **Q=** (b) (4) **at 0.5 hr**
**Q=** (b) (4) **at 2 hr**
**Q=** (b) (4) **at 6 hr**

Reviewer's Comments:

1. Based on the results shown in Figure 2, the proposed dissolution specification for Phen should be changed as follows. It is justified since at 15 min, (b) (4) of Phen was released.

   Change specification for Phen: **From: Q=** (b) (4) **in 30 min**
   **To: Q** (b) (4) **in 15 min**

2. The Agency's proposed dissolution specifications for Tpm are shown below.

Proposed specifications for Tpm: **Q= (b) (4) at 0.5 hr**
**Q= (b) (4) at 2 hr**
**Q= NLT (b) (4) at 6 hr**

The above specifications are based on 1) the overall dissolution data submitted on 07/07/10 for 12 registration lots and 15 clinical lots tested and 2) Agency's IVIVC guidance (p.17), under "Setting Specifications Without IVIVC". The variation (i.e., SD) among the lots is relatively small, therefore, a (b) (4) from the overall means at 0.5 (b) (4), 2 (b) (4) and 6 hrs (b) (4) was employed for setting the ranges of release. A (b) (4) width is not justified due to the low variability observed in the dissolution results.

07/19/10
Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

07/19/10
Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

# NDA 22-580 for Qnexa (Phen IR + Tpm ER) Oral Capsules, 15/92 mg, 11.25/69 mg, 7.5/46 mg, and 3.75/23 mg

# Appendix 1

# Raw and Mean Dissolution Data Submitted on 07/07/10

2 Pages has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

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TIEN MIEN CHEN
07/19/2010

PATRICK J MARROUM
07/19/2010

# NDA 22-580

## QNEXA®
## (phentermine/topiramate)
## Extended Release Capsule

## VIVUS, Inc.

**Joseph Leginus, PhD**
**Division of Pre-Marketing Assessment III, Branch VII, ONDQA**

## For the Division of
## Metabolism and Endocrinology Products

## CHEMISTRY REVIEW #1

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# Chemistry Review Data Sheet

1. NDA 22-580

2. REVIEW #: 1

3. REVIEW DATE: 8-Jun-2010

4. REVIEWER: Joseph Leginus, PhD

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original NDA | 28-Dec-2009 |
| Amendment | 19-Mar-2010 |
| Amendment | 07-May-2010 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | VIVUS, Inc. |
| Address: | 1172 Castro St., Mountain View, CA 94040 |
| Representative: | Peter Tam, President, VIVUS, Inc. |
| Telephone: | 650-934-5309 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: QNEXA®
b) Non-Proprietary Name (USAN): Phentermine/Topiramate
c) Code Name/# (ONDC only): VI-0521; PHEN/TPM Capsules
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4 (New Combination)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.

10. PHARMACOL. CATEGORY:
Combination centrally acting appetite suppressant.

11. DOSAGE FORM: Extended Release Capsule

12. STRENGTH/POTENCY:
QNEXA capsules are manufactured in four strengths (phentermine free base/topiramate): 3.75/23 mg, 7.5/46 mg, 11.25/69 mg and 15/92 mg.[1]

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

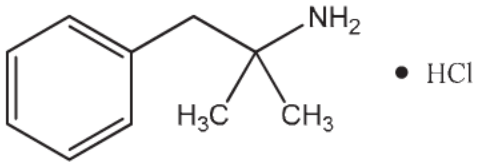
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

A. Phentermine Hydrochloride
Chemical Names: i) Benzeneethanamine-α,α-dimethyl hydrochloride
ii) α,α-Dimethylphenethylamine hydrochloride

Structural Formula:




Molecular Formula: $C_{10}H_{15}N \bullet HCl$

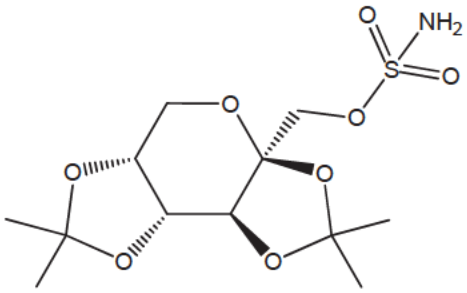
Molecular Weight: 185.69 (hydrochloride salt)
149.23 (free base)

[1] Reference to the dosage strength should be indicated as "x mg/y mg" instead of "x/y mg". However, for the purposes of this review, dosage strengths will be indicated as originally presented by the applicant in the NDA. See Section II. Review of Common Technical Document-Quality (Ctd-Q) Module 1, A. Labeling & Package Insert for recommended changes to the label for dosage strengths.

B. Topiramate

Chemical Names: i) 2,3:4,5-Bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate
ii) β-D-fructopyranose, 2,3:4,5-bis-O-(1-methylethylidene)-sulfamate
iii) 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate

Structural Formula:



Molecular Formula: $C_{12}H_{21}NO_8S$

Molecular Weight: 336.36

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | Type | Holder | Item Referenced | Code[1] | Status[2] | Date Review Completed | Comments |
|---|---|---|---|---|---|---|---|
| (b) (4) | II | | (b) (4) | 1 | Adequate | 12-Dec-2006 | Reviewed by D. Maldonado |
| | II | | | 1 | Adequate | 23-Dec-2009 | Reviewed by L. Hussain |
| | IV | | | 1 | Adequate | 22-Jan-2003 | Reviewed by G. Lunn |
| | III | | | 1 | Adequate | 17-Jul-2007 | Reviewed by D. Klein |
| | III | | | 1 | Adequate | 22-Sep-2004 | Reviewed by S. De |
| | III | | | 1 | Adequate | 05-Jul-2000 | Reviewed by D. Shad |
| | III | | | 1 | Adequate | 24-Sep-2007 | Reviewed by C. Bertha |
| | III | | | 1 | Adequate | 09-Mar-2009 | Reviewed by B. Kurtyka |
| | III | | | 1 | Adequate | 07-Dec-2009 | Reviewed by Y. Tang |
| | III | | | 1 | Adequate | 16-Jul-2004 | Reviewed by L. Hsieh |
| | III | | | 1 | Adequate | 20-Nov-2007 | Reviewed by Y. Sun |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| IND | 68,651 | Phentermine/Topiramate |
| [redacted] | | (b) (4) |
| NDA | 20505 | Topiramate (Topamax) |

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Pending. All facilities are Acceptable except the drug substance (phentermine hydrochloride) manufacturer [redacted] (b) (4) Inspection assigned to Investigations Branch. | [redacted] (b) (4) | N/A |
| Biopharm | A request for the Biopharmaceutics evaluation of dissolution data was made. | 3-Mar-2010 | Albert Chen |
| Methods Validation | Validation may be requested of FDA labs after test methods are finalized. | N/A | N/A |
| EA | Adequate. | 8-Jun-2010 | Joseph Leginus |
| Microbiology | Not required as per ICH Q6A. The solid dosage form has been shown during development not to support microbial viability or growth. | N/A | N/A |

19. ORDER OF REVIEW: N/A

# The Chemistry Review for NDA 22-580

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The recommendation from the standpoint of chemistry, manufacturing and controls is pending a satisfactory response to the deficiencies delineated in the List of Deficiencies and Information Request (in the CMC Review #1 for NDA 22-580).

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

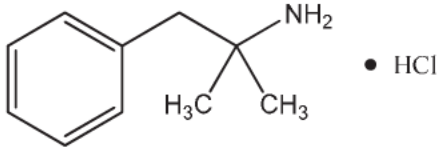
Not applicable.

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCES

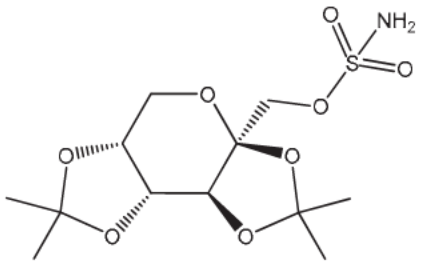
**Phentermine Hydrochloride**
Phentermine hydrochloride (contraction of "**phen**yl-**ter**tiary-butyla**mine**") was approved in 1959 (NDA 11-613) as an appetite suppressant and is currently approved as a generic in several dosage forms including an immediate release capsule (ANDA 088023). It is an amphetamine chemically designated as α,α-dimethyl phenethylamine hydrochloride having the structure shown below.




Phentermine hydrochloride is a white, odorless, hygroscopic, crystalline powder that is soluble in water and alcohols, slightly soluble in chloroform and insoluble in ether. Specifications are based on the USP monograph. In addition, the drug substance is tested for (b) (4). Retest for the drug substance is (b) (4). Information for phentermine hydrochloride is provided in the (b) (4) Type II DMF (b) (4) and is incorporated by reference herein. A copy of the letter of authorization to reference DMF (b) (4) has been provided. DMF (b) (4) was reviewed on 12-Dec-2006 and found to be adequate.

**Topiramate**

Topiramate was approved in 1996 (NDA 20-505, Topamax®) as an anticonvulsant and was approved as a generic in 2006. Topiramate is a sulfamate-substituted monosaccharide, related to fructose, having the following structure:



Topiramate is a white crystalline compound with a bitter taste. It is slightly soluble in water and most soluble in aqueous solutions at pH 9 – 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The specifications for topiramate drug substance conform to the USP Topiramate monograph and also include appearance, (b) (4) melting range and particle size.

Information for topiramate is provided in the (b) (4) Type II DMF (b) (4) and is incorporated by reference herein. A copy of the letter of authorization to reference DMF (b) (4) has been provided. DMF (b) (4) was reviewed on 23-Dec-2009 and found to be adequate.

DRUG PRODUCT

Qnexa® extended release oral capsules are a combination product comprised of immediate-release phentermine hydrochloride beads (PHEN) and extended-release topiramate beads (TPM). PHEN Beads are formulated for (b) (4)

Both bead types are filled into a (b) (4) gelatin capsule as generally illustrated below. No additional excipients are added to the capsules.

(b) (4)

Qnexa capsules are manufactured in four dosage strengths (PHEN/TPM) containing the two drug substances (b) (4). The quantitative composition is indicated as milligrams by weight of phentermine (calculated as the free base) and topiramate as follows:

PHEN/TPM 3.75/23 mg (low dose)
PHEN/TPM 7.5/46 mg (mid dose)
PHEN/TPM 11.25/69 mg (three-quarter dose)
PHEN/TPM 15/92 mg (full dose)

Although the same capsule size (Size 0) is used, each dosage strength is differentiated by a unique combination of capsule colors and printing.

PHEN Beads are manufactured by (b) (4)
(b) (4)

TPM Beads are manufactured by a (b) (4)
(b) (4)

The proposed release specifications include phentermine and topiramate identity (HPLC), assay (HPLC), related substances (HPLC), content uniformity and dissolution; appearance, impurities (b) (4) and microbial limits. All non-compendial regulatory methods have been validated.

Qnexa will be packaged in (b) (4) bottle – at four dosage strengths. (b) (4)

(b) (4)

(b) (4)

Bottled product: The four strengths of Qnexa capsules are separately packaged in (b) (4) high density polyethylene bottles containing 30 capsules (b) (4)

As stated to the applicant (at the 22 July 2009 pre-NDA meeting), the registration drug product batches would be considered the primary stability batches for the purpose of determining an expiration dating period for the product. Of the four strengths, only the highest (PHEN/TPM 15/92 mg) and lowest strengths (PHEN/TPM 3.75/23 mg) were tested for stability based on an acceptable bracketing strategy. The applicant has provided only 8 months of acceptable real time (25°C/60% RH) stability data for the registration batches packaged in (b) (4) bottles. Additional acceptable stability data was generated at an intermediate condition (30°C/65% RH) through six months; however, significant changes to the drug product were observed prior to six months at the accelerated condition (40°C/75% RH) for each strength capsule in (b) (4) bottles. Based on these data, and as detailed in ICH Q1E Evaluation of Stability Data, a shelf-life of 12 months is granted for Qnexa capsules when maintained at the recommended storage condition of 25°C/60% RH.

Vivus, Inc. has submitted an acceptable environmental assessment for Qnexa (b) (4) pursuant to 21 CFR part 25 showing that concentrations of phentermine hydrochloride and topiramate at the point of entry into the aquatic environment are below the threshold value of 1 ppb. As a result, the impact from estimated usage of Qnexa capsules on the environment would be negligible.

## B. Description of How the Drug Product is Intended to be Used

Qnexa extended release capsule is indicated for the treatment of obesity, including weight loss and maintenance of weight loss, in conjunction with diet and exercise. The recommended dose of Qnexa is 7.5/46 mg (phentermine/topiramate), taken once daily in the morning with or without food. Treatment should be initiated using a dose titration starting with the 3.75/23 mg dose for 7 to 14 days followed by the daily dose of 7.5/46 mg. If weight loss goals have not been achieved after 3 - 4 months of treatment, titration from the dose level of 7.5/46 mg to the 15/92 mg dose may be considered. The 15/92 mg dose should be achieved by increasing the daily dose from 7.5/46 mg to 11.25/69 mg for

7 to 14 days prior to increasing the daily dose to 15/92 mg. The drug product will be labeled for long term storage at controlled room temperature (15°C - 25°C; 59°F – 77°F).

**C. Basis for Approvability or Not-Approval Recommendation**

The recommendation from a CMC perspective is pending satisfactory responses to the deficiencies identified in Review #1.

This is a 505(b)(2) application providing for a new extended release combination product (oral capsule). The reference listed drugs (RLD) are Adipex-P (phentermine hydrochloride; ANDA 085128, 088023) and Topamax® (topiramate; NDA 20-505). The associated IND is 68,651 which was received on 11/19/2003. A pre-NDA meeting was held on 7/22/2009.

Drug substance phentermine hydrochloride will be manufactured for commercial use by (b) (4) with most of the CMC parameters provided in the Type II DMF No. (b) (4) A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be adequate.

Drug substance topiramate will be manufactured for commercial use by (b) (4) (b) (4) with most of the CMC parameters provided in the Type II DMF No. (b) (4) A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed and found to be adequate.

The drug product, Qnexa® (phentermine/topiramate) Extended Release Capsule will be manufactured by Catalent Pharma Solutions located in Kentucky, USA as a combination product comprised of phentermine beads (phentermine hydrochloride, (b) (4) and topiramate beads (topiramate, (b) (4) in a size 0 hard gelatin capsule. All excipients comply with corresponding USP and NF monographs. All capsule components have compendial references (gelatin, titanium dioxide), are approved food additives (FD&C colorants) or are food grade quality (printing ink).

A 24 months expiry period for the drug product was requested, however, due to limited stability data (8 months of real time stability provided for the registration batches), an expiry of 12 months will be granted for each of the four dosage strengths of Qnexa in (b) (4) bottles when stored at the recommended storage condition of 25°C.

## III. Administrative

**A. Reviewer's Signature:** in DAARTS
**B. Endorsement Block:** in DAARTS
**C. CC Block:** in DAARTS

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

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/s/

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JOSEPH M LEGINUS
06/08/2010

ALI H AL HAKIM
06/09/2010

**Division of Metabolism and Endocrinology Products**

| | |
|---|---|
| **NDA:** | **22580** |
| **Applicant:** | Vivus Inc. |
| **Stamp Date:** | 28-DEC-2009 |
| **PDUFA Date:** | **28-OCT-2010** |
| **Proposed Proprietary Name:** | Qnexa |
| **Established Name:** | Phentermine hydrochloride and topiramate |
| **Dosage form and strength:** | Capsule: immediate release phentermine and extended release topiramate – 3.75/23, 7.5/46, 11.25/69, and 15/92 (mg/mg phentermine free-base/topiramate) |
| **Route of Administration:** | oral |
| **Indications:** | Treatment of obesity |
| **CMC Lead:** | Su **(**Suong) Tran, Branch II/DPA I/ONDQA |
| **ONDQA Fileability:** | **Yes** |

| CONSULTS/ CMC RELATED REVIEWS | COMMENT |
|---|---|
| Biopharmaceutics | *May Not Be Applicable: No biowaiver request.* |
| CDRH or CBER | *Not Applicable* |
| EA | Categorical exclusion request will be assessed by Primary Reviewer. |
| EES | EER was created and sent to Compliance on 05-JAN-2010 by Don Henry (ONDQA PM) |
| OSE | *Labeling consult request will be sent as part of DMEP's request.* |
| Methods Validation | *Validation may be requested of FDA labs after test methods are finalized.* |
| Microbiology | May be consulted by the Primary Reviewer for input on the microbial limits. |
| Pharm/Tox | Review of the qualification of impurities may be requested if the applicant does not lower their limits to meet the ICH qualification threshold. |

This is an electronic NDA, filed as a 505(b)(2) application, with the reference listed drugs (RLD) being Adipex-P (phentermine hydrochloride), Ionamin (phentermine resin), and Topamax (topiramate) (Note to chemists: the reference is for the reliance on FDA's findings of safety and/or effectiveness only, not for any CMC purpose). The associated IND is IND 68651.

Reference is made to the DMF (b) (4) from (b) (4) for all CMC information on the phentermine hydrochloride drug substance.
Reference is made to the DMF (b) (4) from (b) (4) all CMC information on the topiramate drug substance.

The product is a fixed dose combination (b) (4) gelatin capsule available in the strength of 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg phentermine free-base/topiramate. Each drug substance is formulated as a bead. Each (b) (4) gelatin capsule contains appropriate numbers of the active beads to achieve the desired dosage strengths. The gelatin capsule has color and ink ingredients that comply with food regulations.

(b) (4)

The product will be packaged in (b) (4) 30-count HDPE bottles with (b) (4)
(b) (4)

(b) (4)

**Maximum daily dose is 15/92 mg/mg phentermine free-base/topiramate.**

**Has all information requested during the IND phases, and at the pre-NDA meetings been included?**

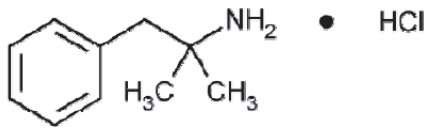
The NDA includes some information as requested by FDA during the IND development. There is no item-by-item response to FDA's comments, which makes it difficult to assess in the limited time allotted for this filing memo/IQA whether the applicant has provided a satisfactory response to each question. The primary reviewer will assess the information in the NDA and decide whether issues previously raised have been satisfactorily addressed. The reviewer will also confirm that information previously agreed upon by FDA and the sponsor has not been changed in its final version in the NDA (for example, specifications, packaging systems, etc.)

Major issues discussed in the FDA letter dated 14-AUG-2009 include:

- Bioequivalence studies are required to bridge the difference between the commercial product formulation (b) (4) and the clinical formulation (b) (4) The biowaiver request was denied by ONDQA.
- Primary (registration) stability batches have the commercial formulation and were manufactured with the commercial drug substances (b) (4) manufactured at least 10% of the commercial scale, and packaged in the commercial container closure systems.
- The NDA should be submitted with a minimum of 12-month long-term stability data. Stability data submitted during the review cycle may or may not be reviewed. A very short expiry may result from having less than the 12-month long-term data in the initial submission.
- A bracketing stability design is acceptable.
- Different phentermine loading levels are acceptable for the different dosage strengths.
- (b) (4) is acceptable for use in the commercial product.

# Drug substance:

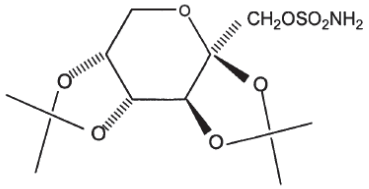
**Figure 1 Phentermine Hydrochloride**




Chemical Formula: C10H15N • HCl Molecular Weight: 185.7

Phentermine hydrochloride drug substance is chemically designated as α, α-dimethyl phenethylamine hydrochloride. It is a white, odorless, hygroscopic, crystalline powder that is soluble in water and lower alcohols; it is slightly soluble in chloroform and insoluble in ether. The chemical structure of phentermine is most similar to that of pseudoephedrine (adrenergic agent) and phenylpropanolamine (adrenergic α-agonist).

**Figure 2 Topiramate Structure - Absolute Stereochemistry**




Chemical Formula: C12H21NO8S Molecular Weight: 339.37

Topiramate drug substance is chemically designated as 2,3:4,5-di-*O*-isopropylidene-ß-D-fructopyranose sulfamate. Topiramate is a white crystalline powder with a bitter taste. It is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and with a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The solubility in water is 9.8 mg/mL.

## Review comments:

- Reference is made to the DMF (b) (4) from (b) (4) for all CMC information on the phentermine hydrochloride drug substance. The primary reviewer will review any new information in the DMF submitted after the most recent review.
- Reference is made to the DMF (b) (4) from (b) (4) for all CMC information on the topiramate drug substance. The primary reviewer will review any new information in the DMF submitted after the most recent review.
- The drug substance specifications are included in the NDA and copied on pages 20-22 of this review. They are based on the USP monographs for these compounds with the additional testing of phentermine HCl for (b) (4)

(b) (4) and additional testing of topiramate for appearance, (b) (4) melting range, and particle size distribution.

- **Polymorphism and particle size**.

(b) (4)

- **Impurities**. FDA's "Guidance for Industry – NDAs: Impurities in Drug Substances" states that ICH Q3A guidelines apply to drug substances that are not new but that are submitted in new NDAs.
    - The applicant proposes a limit of NMT (b) (4) for a single (unknown) impurity in phentermine HCl, which is higher than the ICH identification threshold of 0.10%. This limit should be (b) (4) to meet the ICH threshold (see 74-day letter comment at the end of this review). The applicant justifies the (b) (4) limit by referring to the USP limit in the phentermine HCl monograph, which is the same as the applicant's limit. This justification is not adequate as per FDA's Guidance "NDAs: Impurities in Drug Substances".
    - The topiramate specification has limits of (b) (4) for (b) (4), (b) (4) he applicant justifies these limits by referring to the USP limits in the topiramate monograph which are the same as or higher than the applicant's limits. The (b) (4) limit on (b) (4) is not an issue because this compound is commonly available in prepared and natural food, including fruit.

Based on all available data in the DMFs and NDA and new information to be submitted in response to the 74-day letter comments, the reviewer will decide whether the impurity limits should be lowered to meet the ICH identification and qualification thresholds. If they cannot meet the qualification threshold, appropriate qualification studies will be required and the PharmTox team will be notified. (Potentially genotoxic impurities will be given special consideration as per current FDA's policy.)

# Drug product

The composition of the drug product is copied below.

**Table 2 Composition of PHEN/TPM Capsules**

| Component | PHEN/TPM 3.75/23 mg | PHEN/TPM 7.5/46 mg | PHEN/TPM 11.25/69 mg | PHEN/TPM 15/92 mg |
|---|---|---|---|---|
| PHEN | (b) (4) | | | |
| PHEN | | | | |
| | | | | (b) (4) |
| Printed (b) (4) Gelatin Capsule [a] | one | one | one | one |

[a] (b) (4) gelatin capsule colors are assigned by dosage strength (See Table 5).

(b) (4)

(b) (4)

**Table 5 Composition of Printed (b) (4) Gelatin Capsules**

| Component | Function | % (w/w) | Regulatory References |
|---|---|---|---|
| **Capsules for PHEN/TPM 3.75/23 mg- Purple Body, Purple Cap, White Print** | | | |
| **Body and Cap Composition** | | | |
| (b) (4) | | | CFR21/95/45/EC |
| | | | CFR21/95/45/EC |
| | | | USP/EU/FAO/WHO |
| | | | USP/EU/FAO/WHO |
| | | | Food grade [a] |
| **Capsules for PHEN/TPM 7.5/46 mg- Yellow Body (Black Print), Purple Cap (White Print)** | | | |
| **Body Composition (Yellow)** | | | |
| (b) (4) | | | CFR21/95/45/EC |
| | | | CFR21/95/45/EC |
| | | | USP/EU/FAO/WHO |
| | | | USP/EU/FAO/WHO |
| | | | Food grade [a] |
| **Cap Composition (Purple)** | | | |
| (b) (4) | | | CFR21/95/45/EC |
| | | | CFR21/95/45/EC |
| | | | USP/EU/FAO/WHO |
| | | | USP/EU/FAO/WHO |
| | | | Food grade [a] |
| **Capsules for PHEN/TPM 11.25/69 mg - Yellow Body, Yellow Cap, Black Print** | | | |
| **Body and Cap Composition (Yellow)** | | | |
| (b) (4) | | | CFR21/95/45/EC |
| | | | CFR21/95/45/EC |
| | | | USP/EU/FAO/WHO |
| | | | USP/EU/FAO/WHO |
| | | | Food grade [a] |
| **Capsules for PHEN/TPM 15/92 mg - White Body, Yellow Cap, Black Print** | | | |
| **Body Composition (White)** | | | |
| (b) (4) | | | USP/EU/FAO/WHO |
| | | | USP/EU/FAO/WHO |
| | | | Food grade |
| **Cap Composition (Yellow)** | | | |
| (b) (4) | | | CFR21/95/45/EC |
| | | | CFR21/95/45/EC |
| | | | USP/EU/FAO/WHO |
| | | | USP/EU/FAO/WHO |
| | | | Food grade |
| (b) (4) | | | |

3.75/23 mg controlled release Capsules [Purple cap imprinted with VIVUS, Purple body imprinted with 3.75/23]

7.5/46 mg controlled release Capsules [Purple cap imprinted with VIVUS, Yellow body imprinted with 7.5/46]

11.25/69 mg controlled release Capsules [Yellow cap imprinted with VIVUS, Yellow body imprinted with 11.25/69]

15/92 mg controlled release Capsules [Yellow cap imprinted with VIVUS, White body imprinted with 15/92]

(b) (4)

## Review comments:

- **Established name and dosage strength**. The proposed established names of the product are "phentermine" and "topiramate", which are acceptable because they correlate with the dosage strengths as per current CDER policy on nomenclature. The dosage strength of phentermine is of the free base. The reviewer will ensure that the full amount of the phentermine hydrochloride salt is included in the prescribing information and packaging labels, but it should not have the prominence as the dosage strength.
- **Dosage form.** The product is a fixed dose combination (b) (4) gelatin capsule available in the strength of 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg phentermine free-base/topiramate. Each drug substance is formulated as a bead. Each (b) (4) gelatin capsule contains appropriate numbers of the active beads to achieve the desired dosage strengths. The gelatin capsule has color and ink ingredients that comply with food regulations (information previously requested by FDA).

(b) (4)

(b) (4)

(b) (4)

- **Comparability of the product used in the clinical studies, stability studies, and commercial product**.
    - The formulation of the 3 lower strengths of the commercial product differs from that of the clinical product because the clinical Formulation (b) (4)

      As previously requested by FDA, the formulation difference will be qualified by in vivo studies (see the ClinPharm reviews). The applicant includes comparative dissolution profiles to show that the 2 formulations have no difference in the release of the active ingredients. Because the equivalence of the 2 formulations will be determined by the in vivo results, the review of the comparative dissolution data will not be critical in determining equivalence.
    - The registration stability batches have the commercial Formulation B. As discussed above, the equivalence of this formulation and the clinical Formulation A will be evaluated via in vivo studies. The registration stability batches 0912479 (3.75/23 strength), 0912485 (7.5/46 strength), 0912488 (11.25/69 strength), and 0912482 (15/92 strength) were used in Clinical Study OB-109.
- **Multiple dosage strengths**. All four dosage strengths were used in clinical studies. There is no biowaiver request for any strength.



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

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/s/

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SUONG T TRAN
02/23/2010

PRASAD PERI
02/23/2010
I concur